Medicare Coverage Database

Decision Memo for Infrared Therapy Devices (CAG-00291N)

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Decision Summary

CMS has determined that there is sufficient evidence to conclude that the use of infrared devices is not reasonable and necessary for treatment of Medicare beneficiaries for diabetic and non-diabetic peripheral sensory neuropathy, wounds and ulcers, and similar related conditions, including symptoms such as pain arising from these conditions. Therefore, we are issuing the following National Coverage Determination.

The use of infrared and/or near-infrared light and/or heat, including monochromatic infrared energy (MIRE), is not covered for the treatment, including symptoms such as pain arising from these conditions, of diabetic and/or non-diabetic peripheral sensory neuropathy, wounds and/or ulcers of skin and/or subcutaneous tissues in Medicare beneficiaries.

Decision Memo

TO:	Administrative File: CAG #00291 Infrared Therapy Devices
FROM:	Steve Phurrough, MD, MPA Director, Coverage and Analysis Group Louis Jacques, MD Division Director Karen Rinker, MS Lead Analyst

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SUBJECT: Decision Memorandum for Infrared Therapy Devices

DATE: October 24, 2006

I. Decision

CMS has determined that there is sufficient evidence to conclude that the use of infrared devices is not reasonable and necessary for treatment of Medicare beneficiaries for diabetic and non-diabetic peripheral sensory neuropathy, wounds and ulcers, and similar related conditions, including symptoms such as pain arising from these conditions. Therefore, we are issuing the following National Coverage Determination.

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II. Background

In this section, we describe the technologic developments that gave rise to infrared therapy and discuss the putative mechanisms. We then identify medical conditions for which infrared therapy has been employed, and summarize the pathophysiology epidemiology, societal burden, and standard therapies for these medical conditions. Therapy for a medical condition includes therapy for the symptoms and signs of the condition as well as therapy intended to alter the underlying pathologic process. (Additional discussion of a more technical nature is included in Appendix E.)

A. Historical Background of the Technology

The first operational laser (Light Amplification by Stimulated Emission of Radiation) was developed in 1960 by Theodore Maiman based on work by Charles Townes and Arthur Schawlow (United States) as well as Alekxandr Prokhorov and Nikolay Basov (Soviet Union) (Goldman L, Maiman). This ruby laser produced red light with the unique wave length, 694 nm (nanometers). Robert Hall developed the first semiconductor laser (or laser diode) based on work by Nikolay Basov (Soviet Union) and Ali Javan (Iran) (Dupuis, Hall). This laser utilized gallium arsenide (GaAs) and produced infrared light (850 nm).

Subsequently, non-laser based monochromatic light sources were developed: light emitting diodes (LEDs), supraluminous diodes (SLDs), and polarized polychromatic light. LEDs consist of a chip of semiconducting material that is impregnated with impurities to create a junction for donor electrons and to permit electron current flow (Dupuis). The first LEDs were red and infrared light using gallium arsenide. Later devices employed aluminum gallium arsenide (GaAlAs). Unlike LEDs, true lasers produce light that is collimated (tightly focused) and coherent (in-phase waves). They also have more power and power density. Some of the features that separate lasers and monochromatic other light sources, e.g., coherence, may not be clinically significant. (Karu 1985, 1987, 1989, Lobko, Young). Indeed light coherence is dissipated by a few millimeters of tissue depth (Djibladze, Kolari 1985, 1993, Sroka).

Because of their high power, lasers were initially used in medicine to cut, burn, vaporize, and weld tissue (Abergel, Hall). The use of low level laser (cold, soft, or LLL) therapy was initiated by Dr. Endre Mester (Hungary) in the 1960s (Mester 1968, 1971, 1985). By serendipity, he acquired an underpowered laser that failed to ablate tumor cells implanted in rodents, but which did appear to facilitate healing of the incision sites. Other anecdotal reports, primarily from Eastern Europe and the Soviet Union, suggested utility in a variety of disorders: arthritis, musculoskeletal injuries, nerve disorders, and wound healing (Karu 1987, Ohshiro, Walker). There were reports of accelerated wound healing in Space Station astronauts working on plant experiments involving infrared light (NASA website). Still other anecdotal reports emerged from veterinary practitioners in the 1980s. Indeed some manufacturers provide products for both the human and veterinary medical markets, e.g., Anodyne and Equilight (company websites). Infrared laser (904 nm) was used to treat bowed tendons, check ligaments, chronic back pain, pharyngeal lymphoid hyperplasia, and plantar desmitis (acute and chronic) in uncontrolled observational studies of horses (Martin 1987, McKibben 1983, 1984). Since then, diodes and lasers have been employed off-label for an array of veterinary disorders including equine laminitis (Isabell). Commercial websites are the most common source of these reports (Isabell). The most recent published literature is more rigorous and does not support its use (Peterson).

B. Mechanistic Studies for Technology

The mechanisms by which healing or pain relief might occur are still unknown. The existing information, on its face, is contradictory. For this reason, it has not been possible to identify the specific features of irradiation devices and treatment regimens that are critical to efficacy (See Appendix E for a more in-depth discussion).

C. Disease Summary

1. Peripheral Neuropathy

Peripheral neuropathy may present as a mononeuropathy, mononeuritis multiplex (multi-focal mononeuropathy) (damage to isolated nerves in separate parts of the body), or polyneuropathy (Hughes). Damage may occur at the level of the motor neuron or dorsal root ganglion. Damage may also occur at the level of the axon and its myelin sheath (Wallerian degeneration). The most common forms of peripheral neuropathy affect nerve fibers most distal to the central nervous system. Nerve involvement is symmetric and progresses centrally. Both large and small fibers can be involved. Damage to the large myelin-coated sensory fibers results in diminished fine touch, vibratory sensation, and proprioception. Damage to the large myelin-coated motor fibers results in weakness and wasting. Damage to the small non-myelinated sensory fibers results in diminished temperature sensation and aberrations in pain sensation (paresthesia, dysesthesia, allodynia, or anesthesia).

Peripheral neuropathy may be either inherited or acquired. The most common inherited peripheral neuropathies are the cluster of disorders known as Charcot-Marie-Tooth disease and result from inborn genetic errors of neural structure/function or composition of the myelin sheath. There are many causes of acquired peripheral neuropathy listed below. Physical injury may arise from trauma, repetitive stress, compression from soft tissue or bony structures (e.g., tumor or some forms of spinal stenosis) (Goldman SM). Compression may result from fluid accumulation with acromegaly or hypothyroidism. Toxic effects are produced by heavy metals (e.g., arsenic, lead, mercury, and thallium), medications (e.g., anticonvulsants and antiviral agents), urea, and glucose/end-glycosylation products. Nutritional deficiency, (e.g., vitamin B12, thiamine, and niacin) is also known to cause neuropathy. Infectious causes include Human Immunodeficiency Virus (HIV), Herpes, Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Mycobacterium leprae, and Corynebacterium diphtheriae. Additional causes include abnormal immune responses (e.g., Guillain-Barré syndrome, paraneoplastic syndromes, and chronic inflammation with resultant destruction of connective tissue and increased vulnerability of nerve tissue to compression), and ischemia (e.g., vasculitis and diabetes). Diabetic neuropathy has both toxic and vascular components (Akbari, Archer, Arora, Biessels, Coppey, Kasalova, Kelkar).

Diabetes is a major cause of peripheral neuropathy in the Western World (Gregg). Gregg et al. using NHANES (National Health and Nutrition Examination Survey) data found that 14.8% of people aged 40 years and older had neuropathy (Gregg). The prevalence of neuropathy was 28.5% in diabetic and 13.3% in non-diabetic persons. Conversely, it has been estimated that 12-50% of diabetic patients have some peripheral neuropathy (Nicolucci). Diabetes is also a major cause of painful peripheral neuropathy in the Western World. Backonja estimated that 10% of diabetic patients with peripheral neuropathy had an allodynic (painful) form (Backonja). Cross-sectional surveillance in the United Kingdom found the prevalence of painful peripheral neuropathy to be 16.2% and 4.9% in diabetic and non-diabetic persons respectively (Daousi).

The optimal treatment of peripheral neuropathy requires a correct diagnosis. Treatment of the underlying condition is required. The most common cause of bilateral distal sensory neuropathy, diabetes, appears to benefit from glycemic control although reversal of symptoms may depend on near-normalization of glucose levels for extended periods of time and reversal may be refractory with well entrenched disease (Allen, Azad, Biessels, Britland, DCCT, Isotani, Orloff). The goals of therapy include the relief of pain and improved sensation. Relief of pain should not occur at the expense of sensory function, i.e., destruction of the nerves. Currently, other than glycemic control, we have no treatments for distal diabetic sensory loss (Isotani, Pietri, Predergast 1996).

We do have pharmacologic treatments for pain (Vinik). Off-label therapies include tricyclic antidepressants, e.g., amitriptyline, desipramine and nortriptyline, opioids, and capsaicin cream. Anti-seizure medicines, e.g., carbamazepine and dilantin, have also been used. Carbamazepine has recently been approved for treatment of trigeminal neuralgia. Topical lidocaine 5%, recently approved for post-herpetic neuralgia, has similarly been employed for diabetic neuropathic pain. The first drug approved specifically for diabetic neuropathic pain is duloxetine (Cymbalta®), which is a serotonin and norepinephrine reuptake inhibitor (September 2004). This was followed by pregabalin (Lyrica®), an analogue of gamma-amino butyric acid (GABA) (June 2005). This anti-convulsant medication is approved for 2 types of neuropathic pain: diabetic neuropathic pain and post-herpetic neuralgia. Its chemically related predecessor, gabapentin (Neurontin®), was long used off-label for diabetic neuropathic pain in addition to its approved uses for partial seizures and post-herpetic neuralgia.

2. Skin Ulcers

There are 4 major types of skin ulcers: venous, pressure, ischemic, and neuropathic. Frequently, however, they are not discrete categories. For example, patients with diabetes may initially develop an ulcer because of neuropathy, and subsequent healing is impaired because of diminished arterial perfusion. The cornerstone to the treatment of venous ulcers in the absence of concurrent arterial disease is compression with stockings or other devices. The foundation of treatment for arterial ulcers is revascularization, often through surgery. The therapeutic key for both pressure and neuropathic ulcers is elimination of prolonged pressure. With the exception of ischemic ulcers, all ulcers should be debrided of necrotic and fibrinous debris. This permits good granulation and epithelialization of the wound. Debridement can be done surgically or with dressings.

a. Pressure Ulcers

Pressure ulcers are localized areas of necrosis that develop where soft tissue is compressed for a prolonged time between a bony prominence and an external surface (National Pressure Ulcer Advisory Panel). Pressure ulcers develop when skin pressure exceeds the pressure that occludes capillary flow (Rehm). Prolonged pressure impedes the circulation of blood and lymph, causing a deficit in tissue nutrition as waste products accumulate with tissue ischemia. Ischemia develops after 2 to 6 hours of continuous pressure. Ischemic changes may need 36 hours or longer to resolve. Necrosis develops after 6 hours of continuous pressure. Ulceration occurs within 2 weeks of necrosis.

Pressure ulcers develop in immobilized and elderly patients. The risk of developing pressure ulcers increases dramatically with the presence of intrinsic factors such as immobility, altered level of consciousness, age, chronic systemic disease, and altered nutrition. Excessive moisture removes oils from the skin, making it more friable. Maceration softens the connective tissue of the skin and leads to erosion.

Pressure ulcers affect 1.5 to 3 million Americans (Evans). Nine percent of hospitalized patients develop pressure ulcers (Whittington). Fifteen percent of persons admitted to long-term care facilities have a pressure ulcer at admission, and more than 20% of those admitted without a pressure ulcer develop one within 2 years (Thomas DR, Richardson). Pressure ulcers are associated with a 2- to 4-fold increase in mortality. This increase generally is ascribed to an underlying illness and poor functional status rather than to the ulcer (Evans).

b. Venous Ulcers

Venous ulcers develop in regions of dependent swelling and edema. The source of the edema includes venous incompetency or systemic sources of edema. Patients with heart failure, renal failure, or hepatic failure can present with bilateral edema. Also, medications such as calcium channel blockers, nonsteroidal anti-inflammatory drugs, and cyclooxygenase 2 inhibitors can cause edema. Patients with venous incompetency typically present with unilateral edema (Valencia). Venous ulcers often appear as irregularly shaped wounds along the medial aspect of the leg or in the vicinity of the medial or lateral malleoli. Sustained or recurrent venous hypertension can result in chronic lymphedema, cellulitis, and fibrosis of the ankle joint. Brawny hyperpigmentation is present. The ulcerated skin is often macerated and exudative (London). Approximately 55% of patients with chronic leg ulceration have venous disease (Baker, Nelzen). The prevalence is 0.6-1.6 per 1000. Prevalence is somewhat greater in women and increases with body mass index, but does not increase with age. Venous insufficiency can be expensive when complicated by ulceration.

c. Arterial Ulcers

Arterial ulcers have an ischemic basis. They tend to occur at distal sites (e.g. toes, interdigital web spaces, and the dorsum of the foot) in areas with bony prominences or other features that increase susceptibility to trauma. Typically the ulcers have clear margins and dry, necrotic bases. The affected limbs exhibit loss of skin appendages although nails may be thickened because of impaired keratin turnover. The diagnosis is more evident in patients with frank claudication. Unfortunately, concomitant disease such as angina, arthritis, or chronic obstructive pulmonary disease can reduce physical activity. As such, the ischemia is occult, and the underlying etiology for the ulcer is often initially unrecognized (Newman). The morbidity and mortality of ischemic ulcers is high. The atherosclerotic disease is seldom confined to a single site. Disease is more diffuse and distal when diabetes is present. Patients with atherosclerotic disease, who frequently have multiple risk factors for arterial disease, e.g. age, hyperglycemia, hyperlipidemia, and smoking, are at risk for dying from cardiac or cerebrovascular disease (Hooi). Amputations are more likely. The diagnostic and therapeutic procedures are frequently invasive and contribute to morbidity and mortality. Venous disease and diabetes often coexist in patients with peripheral ischemic vascular disease and are often the original trigger for the ulcer (Andersson).

d. Neuropathic Ulcers

Neuropathic ulcers develop in insensate tissue. In the Western World, the most common cause of insensate tissue is diabetes (Windebank). Less common causes include syringomyelia, leprosy, tabes dorsalis (tertiary syphilis), and drugs including vincristine (Sternman). The lack of sensation facilitates repeated trauma at pressure points such as the first, second, and fifth metatarsal heads, heels, and toes. Callus formation results. Localized ischemia and skin break-down occurs at these pressure points. The lack of sensation prevents discovery of the ulcer, and the callus obscures the depth of the ulcer. Deep ulcers are prone to infection which may involve the bone as well as soft tissue. For these reasons, neuropathic ulcers are frequently serious at the time of presentation (Mantey). The mortality rate is higher in patients with infected neuropathic ulcers than in those with ulcers free of infection (Mantey). Pressure must be relieved from the underlying region of neuropathy and must be eliminated from the area of ulceration (Prabhu).

Pedal ulcers occur in approximately 15% diabetic patients during their lifetime (Boulton 2000, Gonzalez 2000, Kantor 2001, Mancini 1997; NHS Centre for Reviews and Dissemination 1999; Reiber 1999, Spencer, 2002). The point prevalence for foot ulcers in diabetic patients is approximately 6% (Scottish Intercollegiate Guidelines Network 2001). Approximately 76% of diabetic ulcers are primarily neuropathic or neuro-ischaemic in origin (Walters 1992). Up to 15% of all pedal ulcerations terminate in amputation (NHS Centre for Reviews and Dissemination 1999). The incidence rate for amputation is 3-10/1000/year (Gordois). The major burdens of neuropathy are related to ulceration and amputation.

III. History of Medicare Coverage

Prior to this National Coverage Analysis there was no National Coverage Determination (NCD) concerning the use of infrared therapy devices for the indications discussed in this Decision Memorandum. These devices are currently non-covered by the local Medicare Durable Medical Equipment Contractors (DMERCs), which have identical Local Coverage Determinations (LCDs):

> "There are no indications for which these devices have been demonstrated to have any therapeutic effect. The device and any related accessories will be denied as not medically reasonable and necessary."

Available at: http://www.cms.hhs.gov/mcd/viewlcd.asp?lcd_id=12873&lcd_version=9&show=all. (Accessed June 8, 2006)

In drafting this policy in 2002, the DMERCs sent the proposed policy to a number of national professional associations asking for comment:

American Medical Association
American Osteopathic Association
American Academy of Family Physicians (AAFP)
American Academy of Home Care Physicians
American Academy of Neurology
American Academy of Orthopedic Surgeons
American Academy of Physical Medicine and Rehabilitation
American Association of Clinical Endocrinologists
American College of Physicians/ American Society of Internal Medicine
American College of Surgeons
American Geriatric Society
American Orthopedic Foot and Ankle Society
American Podiatric Medical Association (APMA)
American Physical Therapy Association

Only two organizations responded:

APMA said that "the long term effectiveness of these systems has yet to be demonstrated"
AAFP sent a letter saying that they had no comments on the policy

The process used for Medicare contractor local coverage determinations is available at: http://www.cms.hhs.gov/manuals/downloads/pim83c13.pdf. Accessed June 8, 2006.

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. § 1812 (Scope of Part A); § 1832 (Scope of Part B), § 1861(s) (Definition of Medical and Other Health Services). Infrared therapy devices may fall within the benefit category of durable medical equipment (DME), which is referenced in section 1861(s)(6) of the Social Security Act. Infrared therapy also may be provided as services and supplies furnished incident to a physician's service which is referenced in section 1861(s)(2)(A), hospital services incident to a physicians' services rendered to outpatients which is referenced in section 1861(s)(2)(B), and outpatient physical therapy services which is referenced in section 1861(p) of the Social Security Act. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

January 26, 2006	CMS opened an internally generated National Coverage Determination (NCD) to determine that there is sufficient evidence to conclude that infrared devices are reasonable and necessary for treatment of Medicare beneficiaries for diabetic and non-diabetic peripheral neuropathy, wounds and ulcers, and similar related conditions. The initial 30-day public comment period began.
February 26, 2006	End of initial public comment period.
July 26, 2006	CMS posted the proposed decision memorandum on the CMS Web site and invited public comment.
August 25, 2006	End of the second public comment period.

V. FDA Status

A. Product Classification

Some of these devices were previously FDA classified as heating pads. A reader may note reference to heating pads in some contexts.

The products covered in this decision memorandum are discussed in the Federal Register of Regulations, Title 21, Chapter 8, Subpart F, Physical Medicine Therapeutic Devices. Infrared lamps are devices that emit energy at infrared frequencies (approximately 700 nanometers to 50,000 nanometers) and are intended to provide topical heating for medical purposes. They must meet Class II performance standards. There are three subgroups of the FDA product code 890.5500:

FDA product code ILY-Infrared lamp.
FDA product code NHN-Infrared lamp, non-heating, for adjunctive use in pain therapy
FDA product code IOB-Infrared lamp-physical medicine.

B. Labels

The various devices have a variety of labels, but these labels tend to have the following elements:

1. For relaxation of muscles and relief of muscle spasm.

2. For temporary relief of muscle pain.
3. For temporary relief of joint aches, pain, and stiffness that may be associated with arthritis.
4. To temporarily increase local blood circulation.

No red light or infrared light devices have been approved for treatment or management of disease or disease processes including peripheral sensory neuropathy and wounds. FDA approval for such indications would require clinical studies and pre-market approval (PMA). Several of these devices were initially classified as heating pads and their approved indications reflect these roots. For example, SMI, a predecessor to Anodyne, received 510K approval (regulatory class II) for marketing the Spectropad as an electric heating pad in 1994. It was reclassified as an infrared lamp in 2001. The device labeling was limited to:

> "1-Provides heat therapy, i.e., temporarily relieves minor pain, stiffness, and muscle spasm.
> 2-Temporarily increases local blood circulation."

The device sponsor was advised that "any additional claims (e.g. relief of arthritis, tennis elbow, or bursitis) not listed above would constitute a major modification in the use of the device and would require a premarket notification submission (21 CFR 807.81)."

C. Guidance Documents

The FDA has considered the types of endpoints and trial designs that are most appropriate for wound intervention studies. These are delineated in the Draft guidance for industry: Chronic cutaneous ulcer and burn wounds-Developing products for treatment. U.S. HHS Food and Drug Administration, Center for Biologicals Evaluation and Research (CBER), Center for Devices and Radiologic Health (CDRH), and Center for Drug Evaluation and Research (CDER).

> "Wounds differ pathophysiologically, making it difficult-if not impossible-to generalize results obtained from a trial conducted in patients with one type of wound to those with another wound type. Separate safety and efficacy data should be submitted for each wound type for which an indication is sought. A claim of complete wound closure for chronic non-healing wounds is considered the most meaningful of the claims related to wound healing…The clinical benefit of wound closure that lasts for a very brief time is at best, highly limited. In general trials should be designed such that subjects remain on study and continue to be evaluated at least 3 months following complete closure…Measurement of partial healing, if prospectively defined, may document relevant biological activity and be supportive of the determination of efficacy, but cannot be used as primary evidence of clinical efficacy…A claim of accelerated closure reflects a clinically meaningful diminishing of the time until complete closure occurs…Randomization is particularly important to reduce bias in trial for wound indications because standard care wound management procedures and baseline wound characteristics have a profound effect on outcome…It may be important to prospectively stratify randomization by other important covariants...In general, masking (blinding) of patients and investigators to the treatment received will reduce bias and should be employed when feasible."

Available at: hhttp://www.fda.gov/cber/gdlns/ulcburn.pdf. (Accessed 3/10/06)

The FDA does not have a similar published guidance for the development of products for peripheral sensory neuropathy.

D. Warning Letters

Warning letters have been issued to several device makers. Most of the letters were issued for making claims beyond the FDA clearance. The claims at issue required clinical studies and pre-PMA by the FDA. One manufacturer was cited for marketing without 510K approval or a PMA as well as unsafe study conduct. Two manufacturers were cited for manufacturing issues. One manufacturer was cited for the failure to have an adequate patient safety monitoring system in effect and for failure to properly investigate and report burns resulting from the device. (See Appendix F).

E. Adverse Events

This discussion has been updated to include additional adverse events that have been reported since the proposed decision memorandum was written.

The FDA Manufacturer and User Facility Device Experience (MAUDE) adverse event surveillance system revealed 50 (or 51) patients with burns after Anodyne® therapy. (One reporter described 2 lesions, but did not clarify whether they occurred in 1 or 2 patients.) Twelve patients incurred burns using the Model 120 home unit. Thirty-seven (or 38) patients received burns after receiving treatments by a health care professional using the Model 480 professional unit. One patient was burned after using the MPO21300 unit. All reports occurred after 2002. Some patients developed multiple small blisters whereas others had extensive areas of involvement, e.g., 8 x 4.5 cm. At least 1 patient required skin grafting. At least 3 patients developed burns after falling asleep with the unit in place, but some patients developed burns during 30 minute treatment periods. Although most burns were located on the legs and feet, burns of the hand, forearm, shoulder, chest, and hip were also reported. There appeared to be multiple causes for the burns including cleaning problems resulting in device corrosion, broken wires or solders, and external weight or pressure applied to the LED pads.

An engineer received a shock from an Anodyne® device. Per the report, multiple problems contributed to this including defects in the internal insulation, incomplete grounding, lack of a “medical isolation” transformer, and insufficient distance between brass screws and the “phono” plug.

No burns were identified for other related products. There were 3 reports of abnormal sensation (buzzing, electrical stimulation, or flushing) with devices from Bales Scientific. There was 1 report of headache, impaired neck mobility, pain, and swelling and 1 report of lack of efficacy with Light Force therapy devices. There was a single report of a dermal infection after 3 weeks of use of a Bioscan Light device to accelerate healing. Whether the predominance of adverse event reports for Anodyne® reflects market share or specific features of its products is unknown.

Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail. (Accessed 4/10/06 and 9/20/06)

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We are providing a summary of the evidence that we considered during our review. The evidence reviewed in this NCA includes the published medical literature on pertinent clinical trials of light therapy for wounds and peripheral sensory neuropathy.

B. Discussion of evidence reviewed

1. a. Questions

> *1. Is the evidence sufficient to determine that infrared therapy improves health outcomes in Medicare beneficiaries with skin wounds or skin ulcers?*
>
> *2. Is the evidence sufficient to determine that infrared therapy improves health outcomes in Medicare beneficiaries with peripheral sensory neuropathy?*
>
> *3. If the answer to Question 1 and/or Question 2 above is affirmative, what characteristics of the patient, the disease, or the treatment reliably predict a favorable health outcome?*

b. Outcomes

We preface our consideration of the questions with a discussion of the evidence regarding appropriate outcomes (endpoints) for trials of peripheral neuropathy, hypoesthesia (which may result from peripheral neuropathy), and skin ulcers and wounds, based on published clinical literature.

<u>A. Optimal Study Design and Endpoints</u>

The goals of therapy are the reduction of pain, the reversal of hypoesthesia, improved skin ulcer and wound healing, and the reduction of the complications of neuropathy, skin ulcers, and wounds.

<u>1. Neuropathic pain:</u>

> *a. Trial Populations: Studies should avoid inclusion of a heterogeneous patient population.*
>
> > i. Routine clinical laboratory testing should be undertaken to help identify the etiology of the neuropathic disease. Patients with type 1 diabetes should be studied separately from patients with type 2 diabetes because the etiology of the neuropathy may differ. With the latter group, ischemia may be more contributory than glucose toxicity (Kasalova, Sima 1988, 1996).
> >
> > ii. Quantitative sensory threshold testing (QST) should not be used solely in the diagnosis of pain syndromes because of the complex psychosocial aspects of pain and because the QST is not infallible in

detection of malingering (Shy).

iii. Idiopathic small fiber neuropathy should be excluded with nerve conduction studies because its clinical course may differ from that of large fiber neuropathies (Shy).

iv. There should be stratification or adjustment for age, current glycemic control, prior glycemic control, and duration of diabetes. Changes in glycemic control should be avoided during the clinical trial and in the interval prior to study entry (Adler, Boulton 2005, Windebank).

b. Endpoints

i. Pain reduction should be measured by quantitative methods that have been well validated. There are limitations with the current instruments for diabetic pain. There are few instruments for assessment of non-diabetic neuropathic pain.

ii. The amount of pain reduction should be biologically significant.

iii. Pain reduction should not occur at the expense of nerve tissue function and viability.

2. Hypoesthesia:

a. Trial Populations: Studies should avoid inclusion of a hetergeneous patient population although this may be difficult given the current level of diagnostic certainty.

i. There is no single diagnostic reference standard for large fiber distal symmetric polyneuropathy, or even the most rigorously studied subtype, diabetic peripheral neuropathy (England).

ii. Multiple clinical deficits are more predictive of true neuropathy than a single deficit (England, Franse).

iii. A combination of neuropathic symptoms, signs, and electrodiagnostic studies imparts the most accurate diagnostic categorization of patients. Composite tests with high sensitivity and specificity include the Michigan Neuropathy Screening Instrument (MNSI), the Michigan Diabetic Neuropathy Score (MDNS), the Neuropathy Disability Score (NDS), as well as the instruments developed by Franklin et al., Meijer et al., and Valk et al. (Bril, England, Franklin, Meijer 2002, 2005, Valk).

iv. The nerve conduction study is the most important electrodiagnostic test. Abnormal conduction results ($\leq 1^{st}$ percentile, $\geq 99^{th}$ percentile) markedly improve the specificity of composite tests.

v. QST alone is an insufficient diagnostic parameter (Dyck 1990, 1995, England, Feldman). QST abnormalities may be detected in the absence of clinical pathology, and it not known whether the presence of such abnormalities is predictive of progression to clinical neuropathy (Shy).

vi. Monofilament testing, although useful in clinical practice and in epidemiologic cross-sectional surveys, has not been validated for use in longitudinal intervention studies (McGill 1998, 1999, Olmos, Rith-Najarian, Weinstein).

vii. Until there are better markers for disease, research trial enrollment should be limited to patients with high likelihood of true disease (England).

viii. Patients with type 1 diabetes should be studied separately from patients with type 2 diabetes because the etiology of the neuropathy may differ. With the latter group, ischemia may be more contributory than glucose toxicity (Kasalova, Sima 1988, 1996).

ix. There should be stratification or adjustment for age, current glycemic control, prior glycemic control, and duration of diabetes. Changes in glycemic control should be avoided during the clinical trial and in the interval prior to study entry (Adler, Boulton 2005, Windebank).

b. Endpoints

i. Diagnostic imprecision, limited validation in longitudinal studies, and poor clinical correlative or predictive value for many of the current measurement tools of sensory change suggest that hard clinical endpoints, and not surrogate markers, should be employed. Such endpoints would include the rates of new neuropathic ulcers and amputation.

ii. Fall rates could provide useful data, but would be difficult to document and quantitate. Determining the fracture rate (wrist, hip) from falls due to insensate feet would be less ambiguous clinical endpoint.

iii. Surrogate markers may be useful primary endpoints in pilot studies and as secondary endpoints in definitive trials, but the reversal of hypoesthesia should be measured by quantitative methods. The quantitative methods should assess multiple aspects of tactile function. The quantitative methods should not be affected by operator variables. The quantitative methods should be minimally impacted by subject reaction time and subject attention span (Shy). The level of anesthetic reversal should be biologically significant.

<u>3. Skin Ulcers and Wounds:</u>

a. Trial Populations: Studies should avoid inclusion of a heterogeneous patient population.

i. Patients with 1 type of ulcer should be studied separately from patients with other types of ulcers because the etiology differs. Patients with mixed types of ulcers should be excluded in initial pilot studies because it may introduce imbalance at baseline and complication interpretation of results in small studies.

ii. There should be stratification or adjustment for age, ulcer size, duration of refractory treatment, and nutritional status (Margolis 2000, 2004, Takahashi).

b. Endpoints

i. The time-to-complete closure and the percent of patients with complete closure are hard endpoints. These endpoints are more clinically important than healing velocity alone (FDA guidance). Furthermore these endpoints are not subject to the problems of serial size measurements with poorly validated tools.

ii. The recurrence of ulceration 3 to 12 months after complete closure assesses the robustness of the replacement tissue. Patients with one type of ulcer should be studied separately from patients with ulcers of a different etiology.

iii. The amputation rate for non-healing ulcers is a hard endpoint that would yield important clinical information for the Medicare population because of its impact on the capacity to function independently (Frieden).

iv. Hospitalization rates could provide useful data, but are subject to bias.

2. External Technology Assessments and Reviews

Insurance Carriers

a. Blue Cross/Blue Shield of Wisconsin

Skin Contact Monochromatic Infrared Energy Therapy (MIRE)
Policy MED.00050 (Revised 7/14/2005)

“Skin contact monochromatic infrared energy therapy (MIRE) involves the use of superluminous light to topically treat various conditions. This policy addresses the use of MIRE for all indications. Skin contact monochromatic infrared energy therapy, including, but not limited to, the Anodyne Therapy™ system, is considered investigational/not medically necessary as a technique to treat all indications, including, but not limited to, musculoskeletal conditions, diabetic neuropathy, cutaneous ulcers, or lymphedema.”

Low Level Laser Therapy
Policy MED.00043 (Revised 7/14/2005)

“This policy addresses low level laser therapy (LLLT), which uses laser devices producing laser beam wavelengths between 600 and 1000 nm and watts from 5-500 milliwatts (mW). This policy addresses the use of LLLT for all indications. The use of low level laser therapy, also referred to as cold laser therapy, is considered investigational/not medically necessary for all indications, including, but not limited to, carpal tunnel syndrome, Raynaud's phenomenon, fibromyalgia, other musculoskeletal disorders, chronic non-healing wounds, and neurological dysfunctions. As part of the FDA approval process, the manufacturer of the MicroLight device conducted a double blind placebo controlled study of 135 patients with moderate to severe symptoms of carpal tunnel syndrome who had failed conservative therapy for at least a month. However, the results of this study have not been published in the peer-reviewed literature and only a short summary is available in the FDA Summary of Safety and Effectiveness, which does not permit scientific conclusions.”

Available at: http://www.bcbswi.com. (Accessed 3/6/06)

b. Aetna

Clinical Policy Bulletin #0604 for Infrared Therapy
(Updated November 22, 2005)

ICD-9 Codes not covered for indications listed in the Clinical Policy Bulletin

250.60 - 250.63	Diabetes with neurological manifestations
357.2	Polyneuropathy in diabetes
457.0	Postmastectomy lymphedema syndrome

457.1	Other lymphedema
757.0	Hereditary edema of legs
870.0 - 897.1	Open Wounds
998.31 - 998.32	Disruption of operation wound
998.83	Non-healing surgical wound

Available at: http://www.aetna.com/cpb/data/CPBA0604.html. (Accessed 3/6/06)

Research or Government Agencies

a. Wound Care

i. Laser therapy for venous leg ulcers (Cochrane Review).
The Cochrane Library, Issues 1, 1999 and 3, 2002. Oxford, UK. (Flemming 99a, 99b, 02)

“There is insufficient evidence in this review to give a clear direction for practice. There is no evidence of a benefit of lasers on leg ulcer healing, though there is not clear evidence of no benefit as the trials are small and of poor quality.”

“We have found no evidence of any benefit associated with low level laser therapy on venous leg ulcer healing. One small study suggests that a combination of laser and infrared light may promote the healing of venous ulcers, however, more research is needed.”

Available at: http://www.update-software.com/Abstracts/ab001182.htm. (Accessed 3/6/06)

ii. Wound-healing technologies: Low-level laser and vacuum-assisted closure. Evidence Report.
Agency for Healthcare Research and Quality (AHRQ) Publication No. 05-E005-2. Dec 2004. Rockville, MD. (Samson)

“Overall, the quality of this body of evidence is poor, and does not permit definitive conclusions. However, the available data suggests that the addition of laser therapy does not improve wound healing, as the vast majority of comparisons in these studies do not report any group differences in the relevant outcomes. It is unlikely that the lack of significant differences is the result of a type II error, since there are no trends or patterns that favor the laser group.”

Available at: http://www.ahrq.gov/clinic/tp/woundtp.htm. (Accessed 3/10/06)

iii. Low level laser therapy for wound healing.
Alberta Heritage Foundation for Medical Research (AHFMR); 1999: 1-23 and 2004: 1-34. Edmonton, AB. (Simon, Schneider)

“To date, neither Health Canada nor the US Food and Drug Administration have approved low energy lasers for use in wound healing. Systematic reviews of the literature indicate that the efficacy of LLLT in this application is not established although it poses little or no safety risk to patients. There is no good scientific evidence to support its use and mounting evidence to indicate it does not benefit wound healing. Any local use of LLLT in this application should be limited to research in patients resistant to conventional therapy."

Available at: http://www.ahfmr.ab.ca/publications. (Accessed 3/6/06)

iv. Low level laser therapy (LLLT). Technology Assessment.
Washington State Department of Labor and Industries, Office of the Medical Director; May 3, 2004. Olympia, WA. (Wang)

"Low level laser therapy is a noninvasive treatment that has been used for many conditions. While researchers have published extensively on LLLT, the trials have generally been small, do not compare LLLT to alternative therapies, and apply a range of treatment parameters. In several trials the placebo control groups have improved as much as active laser groups. Therefore the evidence has not substantially shown the effectiveness of LLLT."

"Pooled analyses concerning wound healing have not detected any improvement of active laser compared to placebo. The evidence has not shown LLLT to be effective in the treatment of venous wounds."

Available at: http://www.lni.wa.gov/ClaimsIns/Providers/Treatment/TechAssess/default.asp. (Accessed 3/6/06)

b. Neuropathy

i. Photonic stimulation for the treatment of chronic pain.
Canadian Coordinating Office of Health Technology Assessment (CCOHTA). Pre-assessment No. 11. November 2002. Ottawa, ON.

"A more comprehensive literature search would be required before definitively stating that there is no reliable evidence of photonic stimulation for the treatment of chronic pain. However, the results from preliminary searches and the work of others indicate that further searches would not likely find sufficient high quality evidence upon which to base an assessment of this technology."

Available at: http://www.ccohta.ca/publications/pdf/ 238_No11_photonic_stimulator_preassess_e.pdf – Microsoft Int. (Accessed 3/6/06)

ii. Anodyne Therapy System (Anodyne Therapy LLC) for Peripheral Neuropathy.
Hayes Brief. 6/6/05. Hayes Search and Summary 2/15/05
Monochromatic phototherapy for diabetic neuropathy.
Technology Assessment Brief in Hayes Alert. Vol 6(2) Feb 2003. Pages 7-8.

"The Anodyne system is owned and manufactured by Anodyne Therapy LLC…In August 2000, the Medassist Group obtained exclusive distribution rights for the Anodyne Therapy System…MIRE delivered by the Anodyne system is intended for the treatment of patients with symptoms resulting from diabetic neuropathy, other peripheral neuropathies, lymphedema, non-healing wounds, and pain syndromes… Treatment protocol includes 20-45 minute sessions once or twice daily, 3 to 7 times per week for all wounds or areas with decreased sensation…No special credentialing issues regarding the use of the Anodyne Therapy System were identified."

"Data from 5 peer reviewed, published studies suggests that the delivery of MIRE by the Anodyne Therapy System results in significant short-term improvements in nerve function and symptoms of peripheral neuropathy such as sensory impairment in a patients, and that treatment could reduce the occurrence of foot wounds and problems with balance. However, definitive conclusions regarding the efficacy of this therapy cannot be made due to limitations in study design including small sample sizes in all but 1 retrospective chart review, a lack of controls in most studies, and a lack of comparison with standard therapies. None of the studies demonstrates convincingly that this therapy leads to improved long-term health outcomes. Since most of the patients had diabetic neuropathy, evidence regarding treatment of neuropathy associated with other causes is minimal. No complications were reported in the reviewed studies. Recommendation: Current evidence regarding the safety and efficacy of the Anodyne Therapy System for treatment of peripheral neuropathy is negative or insufficient and does not support adoption or use."

iii. Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. (Cochrane Review.) The Cochrane Library. # CD003219. Issue 1, 2003. Oxford, UK. (O'Connor)

"Other Cochrane reviews show benefits from nerve decompression surgery and steroids. This review of other non-surgical treatments found some evidence of short-term benefit from oral steroids, splinting/hand braces, ultrasound, yoga and carpal bone mobilization (movement of the bones and tissues in the wrist), and insulin and steroid injections for people who also had diabetes. Evidence on ergonomic keyboards and vitamin B6 is unclear, while trials so far have not shown benefit from diuretics, non-steroidal anti-inflammatory drugs, magnets, laser acupuncture, exercise, or chiropractic."

Available at: http://www.update-software.com/Abstracts/ab003219.htm. (Accessed 3/6/06)

iv. Position paper on low level laser therapy (LLLT). Medical Position Papers. Ohio Bureau of Workers' Compensation. September 2004. Columbus, OH.

"Preliminary reports of LLLT to treat carpal tunnel syndrome and other musculoskeletal disorders have been positive but randomized controlled trials have not demonstrated effectiveness of the treatment except in one study by Naeser with only 11 participants."

Available at: http://www.ohiobwc.com/provider/services/medpositionpapers.asp and http://ww.ohiobwc.com/downloads/blankpdf/PositionLaserTherapy.pdf. Accessed 3/6/06.

v. Low level laser therapy (LLLT). Technology Assessment.
Washington State Department of Labor and Industries, Office of the Medical Director; May 3, 2004. Olympia, WA. (Wang)

"Low level laser therapy is a noninvasive treatment that has been used for many conditions. While researchers have published extensively on LLLT, the trials have generally been small, do not compare LLLT to alternative therapies, and apply a range of treatment parameters. In several trials the placebo control groups have improved as much as active laser groups. Therefore the evidence has not substantially shown the effectiveness of LLLT."

"Due to the lack of published trials, LLLT for CTS is considered investigational." (CTS is carpal tunnel syndrome.)

Available at: http://www.lni.wa.gov/ClaimsIns/Providers/Treatment/TechAssess/default.asp. (Accessed 3/6/06)

3. Internal Technology Assessments

Systematic reviews are based on a comprehensive search of published studies to answer a clearly defined and specific set of clinical questions. A well-defined strategy or protocol (established before the results of the individual studies are known) guides this literature search. Thus, the process of identifying studies for potential inclusion and sources for finding such articles is explicitly documented at the start of the review. Finally, systematic reviews provide a detailed assessment of the studies included.

a. Literature Search Methods

CMS staff extensively searched MedLine (1965 to present) for primary studies evaluating the use of infrared light therapy for peripheral sensory neuropathy and dermal ulceration. CMS staff likewise searched the Cochran Collaboration, the NHS (National Health Service [GB]) Centre for Reviews and Dissemination, and the INAHTA (International Network of Agencies for Health Technology Assessment) databases for all systematic reviews and technology assessments. Systemic reviews were used to identify some of the obscure studies. Unpublished data were not included. Keywords used in the search included: laser and wound, laser and ulcer, laser and neuropathy, diode and wound, laser and pain, diode and ulcer, diode and neuropathy, diode and pain, infrared and wound, infrared and ulcer, infrared and neuropathy, infrared and pain, photonic therapy and wound, photonic therapy and ulcer, photonic therapy and neuropathy, and photonic therapy and pain.

Preference was given to English language publications, but, because pivotal work was conducted in eastern Europe, translations of critical studies were obtained. Randomized clinical trials were given greater weight than case series and studies in which patients served as their own control. Trials published as full length articles in peer reviewed journals were given greater weight than abstracts or trials with incomplete data. Studies with larger, defined patient populations were given greater weight than small pilot studies in which the intervention was employed for a variety of disorders. Studies with clinical outcomes were given greater weight than studies with surrogate endpoints.

CMS staff also reviewed the literature, professional society consensus statements, and FDA guidance documents for information on the most appropriate diagnostic tools and endpoints in longitudinal intervention trials for wounds and peripheral sensory neuropathy. CMS staff review of additional materials provided through the public comment process on the proposed decision memorandum is included in the revised Findings section below.

b. Findings

Despite an exhaustive search, we identified no high quality, randomized, phase III trials with hard clinical endpoints for either dermal wounds or peripheral sensory neuropathy. Furthermore, none of the small randomized studies support the use of infrared light. (See Appendix B for a schematic diagram and Appendix C for evidence tables.)

We identified 54 publications in which infrared and/or red light was used for the treatment of cutaneous wounds or peripheral sensory neuropathy. Thirty-four could be accessed via MedLine. Thirty-three of the studies (29 for wounds; 4 for neuropathy) were performed outside the U.S. Twenty-one studies documented institutional ethics board approval (n = 7), proper informed consent, (n = 4), or both (n = 10).

Wounds or Skin Ulcers: Search

Forty of the 54 identified publications addressed light therapy for wound management. Of these, 7 were abstracts, and 33 were full length articles. Two full length manuscripts by Kleinman and Gupta et al. later incorporated the work from 2 abstracts by Braskma and Telfer et al. respectively (Braksma, Gupta, Kleinman b, Telfer). There were 3 additional duplications (Franek, Kokol, Kopera a, b, Krol). The study by Kopera et al. was published 3 times; twice in English-language journals and once in a German-language journal (Kokol, Kopera a,b). The study by Krol et al. appears to be based on a smaller series of patients that was incorporated into a larger study by Franek et al (Franek, Krol). After correcting for these duplications, there were 35 unique studies of light therapy for wound treatment. A variety of wounds were studied by the investigators. Fourteen of the studies assessed venous ulcers, 6 pressure ulcers, 5 diabetic ulcers, and 3 post-operative wounds, whereas 6 studies assessed patients afflicted with wounds due to an assortment of causes and 1 study assessed patients with "diabetic venous stasis ulcers".

The studies utilized a variety of devices and wavelengths. Sometimes the light was monochromatic. Other times the light was polychromatic; either as continuous spectral light or as a combination of monochromatic spectra. Of the 14 studies of venous ulcers, only 4 studies had a treatment arm utilizing devices that emitted infrared light alone (wavelengths $\geq$ 730 nm) (Franek, Kleinman b, Malm, Sugru). The remainder of the studies used infrared light in conjunction with red light (n = 3) (Clements, Gupta, Lagan 2002), red light alone (n = 4) (Brunner, Kopera a,b, Lundeberg, Santoianni), or did not indicate the frequency of the light therapy (n = 2) (Crous, Bihari). One study used red light for 1 year of the study (n=42) and infrared light for the subsequent year (n=20) and did not separate the patients in the analysis. The 1 study of "diabetic venous stasis ulcers" used infrared light in conjunction with red light (Lanzafame).

Of the 6 studies of pressure ulcers, only 3 utilized devices emitting infrared light alone (Lievens, Lucas 2000, 2003). The 3 remaining studies used infrared in conjunction with red light (Nussbaum, Schubert, Taly).

Of the 5 studies of diabetic ulcers, none employed devices radiating only infrared light. Three of the studies used infrared in conjunction with red light (Lagan 1996, Landau 1998, 2001). One did not indicate the frequency of the light therapy (Powell 2004). One study used infrared therapy with or without red light therapy and/or topical hyperbaric oxygen therapy and did not distinguish between treatment arms when presenting the results (Kleinman a).

Of the 3 studies of surgical wounds, 2 utilized devices emitting only infrared light (Lagan 2001, Palmgren). One study used infrared in conjunction with red light (Iusim).

Of the 6 studies of assorted wounds, 3 utilized devices emitting only infrared light (Horwitz, Kawalec, Kubota). Two studies used red light (Gogia, Schindl 1999). One study did not indicate the wavelength of the light (Shuttleworth).

In summary there were 12 studies of wounds in which the efficacy of infrared therapy could potentially be assessed because infrared therapy was used alone and not in conjunction with other light wavelengths or experimental therapies (Franek, Horwitz, Kawalec, Kleinman b, Kubota, Lagan 2001, Lievens, Lucas 2001, 2003, Malm, Palmgren, Sugru).

Of these 12 studies of wounds in which there was an infrared monotherapy arm, 6 were placebo-controlled with a contemporaneous parallel group (Franek, Lagan 2001, Lucas 2000, 2003, Malm, Palmgen). Indeed one of these studies employed 2 controls, 1 sham control and 1 unblinded control (Franek). Among the 6 studies without a contemporaneous parallel control group, 4 used patients as their own control (Kawalec, Kleinman b, Lievens, Sugru) whereas the 2 others, including 1 initially planned as a prospective controlled trial (Horwitz), were case series with 5 patients each (Horwitz, Kubota).

Of the 6 contemporaneously placebo controlled studies, 5 were double- or single-blinded (Franek, Lucas 2000, 2003, Malm, Palgrem) and 3 investigative teams reported using portable sham devices (Franek, Malm, Palgrem). These 6 studies were structured to assess the change in ulcer size over short intervals. Placebo controlled treatment periods ranged from 6 to 12 weeks (Lagan 2001, Lucas 2000, 2003, Malm), but were unspecified in 2 studies (Franek, Palmgren). None of the studies were designed to assess the time-to-complete-closure and the frequency of skin breakdown 3 to 6 months after complete closure. The 6 trials evaluated only 4 monochromatic spectra (810, 820, 830, and 904 nm). None of the investigators explored other therapeutic regimens with different wavelengths, pulsatility, and duty cycles. None of the investigators undertook dose ranging studies for energy density, frequency of dosing, and duration of dosing. Study sizes were small – with 9 to 86 patients (Franek, Lagan 2001, Lucas 2000, 2003, Malm, Palmgren).

Wounds or Skin Ulcers: Summary of Reported Results

Results reported in individual studies are described in the evidence tables in Appendix C. The controlled trials did not demonstrate any benefit from infrared therapy for wound healing –regardless of the type of wound. More specifically, there were no differences in wound size or the percent of healed wounds between the treatment and control arms in 2 studies of venous ulcers (Franek, Malm). Indeed, the study by Franek et al. employed both a sham control and an unblinded control. Likewise there were no differences in wound size between treatment and control groups for either of the 2 studies of pressure ulcers (Lucas 2000, 2003). Serial measurement of Norton scores suggests that the absence of difference was not attributable to differential changes in skin ulcer risk (Lucas 2003). For surgical wounds, Lagan et al. reported no differences in wound size change or pain between the treatment and control groups (Lagan 2001). Although Palmgren et al. reported more rapid rates of healing for surgical wounds after infrared therapy, no statistical data were provided (Palmgren). There were no controlled studies of infrared monotherapy for diabetic wounds and wounds of other etiologies.

Peripheral Neuropathy: Search

Fourteen of the 53 publications addressed light therapy used for the anesthesia, dysthesia, or pain of peripheral neuropathy. All but 1 of the publications were full length articles. There were no duplicate articles although the Powell 2005-06 study of neuropathy and the Powell 2004 study of wounds employed similar patient databases. Nine of the studies assessed presumed diabetic neuropathy; no additional testing was done to exclude other causes (Arnall, Clifft, DeLellis, Jie, Kochman 2002, Leonard, Pappas, Powell 2005-06, Yongzhan). One study assessed painful diabetic neuropathy characterized by the Toronto Clinical Neurology Score (Zinman). Four of the studies assessed peripheral neuropathy from a variety of causes (Harkless, Kochman 2004, Predergast 2004, Volker).

Of the 14 studies of peripheral neuropathy, 11 utilized infrared light alone in a treatment arm (Clifft, DeLellelis, Harkless, Jie, Kochman 2004, Leonard, Pappas, Predergast 2004, Volker, Yongzhan, Zinman). One study used a light source emitting both red and infrared light (Arnall). The remainder of the studies did not indicate the frequency of the light therapy (Powell 2005-06, Kochman 2002). Of the 11 studies of peripheral neuropathy in which there was an infrared monotherapy arm, 3 were placebo controlled with a contemporaneous parallel group (Clifft, Leonard, Zinman). For 7 studies without a contemporaneous parallel control group, patients served as their own control (DeLellis, Harkless, Jie, Kochman 2004, Pappas, Predergast 2004, Volker, Yongzhan). All 3 of the contemporaneously placebo controlled trials were double-blinded and used sham devices (Clifft, Leonard, Zinman).

Of the studies with a contemporaneous control group, 2 employed visual analog scoring to assess pain (Leonard, Zinman). Three of the studies employed monofilaments for pressure assessments (Clifft, Leonard, Zinman), but only 1 employed calibrated monofilaments (Zinman) and only 1 assessed vibratory and temperature sense losses in addition to nerve conduction velocity (Zinman). None of the studies reported use of forced-choice algorithms for sensation testing. None of the studies used hard clinical endpoints such as ulceration or amputation rate. The placebo controlled treatment periods were limited to 2 (Leonard) and 4 weeks (Clifft, Zinman). One study employed a pre-treatment blinded sham therapy period (Zinman), and 2 studies employed 2 to 4 week post-treatment sham withdrawal (Clifft 4 weeks; Zinman 2 weeks). In the remaining study, the 2 week placebo controlled phase was followed by an unblinded two week active treatment extension period in which infrared therapy was actively applied to both extremities (Leonard). None of the studies assessed long-term durability of any treatment effect. The 3 trials evaluated only 2 monochromatic spectra (890 and 905 nm). None of the investigators explored other therapeutic regimens with different wavelengths, pulsatility, and duty cycles. None of the investigators undertook dose ranging studies for energy density, frequency of dosing, and duration of dosing. Study sizes were small with 18, 43, and 50 patients respectively (Clifft, Leonard, Zinman).

Peripheral Neuropathy: Summary of Reported Results

Results reported in individual studies are described in the evidence tables in Appendix C. The trial results did not demonstrate benefit for the use of infrared therapy for peripheral sensory neuropathy. Indeed, in the most recent study, Clifft et al. reported a statistically significant increase (~ 40%) in calibrated monofilament sensitivity over baseline after 4 weeks of treatment for the completers in both the active treatment and sham treatment groups (intent-to-treat data were not presented) (Clifft). This was followed by the absence of significant changes in monofilament sensitivity after an additional 4 week period without treatment. Of note, 2 of the patients incurred superficial burns under the device pads.

Similarly, Zinman et al. reported 18% and 22% pain score reductions in active and control patients respectively during the sham treatment run-in of the study. Changes in the pain scores during blinded treatment phase, however, did not differ between groups. In addition, changes in pain scores did not differ between groups after a 2 week withdrawal of any treatment. The results for other study parameters, the Toronto Clinical Neurology Score, quantitative sensory testing, and nerve conduction studies, reportedly did not change during the course of the study. (The numeric data were not published).

A third group of investigators, Leonard et al., reported different patients responses depending on the severity of the neuropathic hypoesthesia. They did not observe any improvement in monofilament sensation after either 6 or 12 weeks of treatment for patients with more severe sensory loss (insensate to the 6.65 monofilament) (Leonard). They, however, did report cumulative sensory improvement (46%) after 2 and 4 weeks of active treatment in the less severely affected patients (sensate to the 6.65 monofilament). Monofilament sensation for the sham treatment group also reportedly improved progressively after 2 weeks of sham treatment (~ 17%) and another 2 weeks of active treatment (~ 20%) after cross-over. The statistical calculations, however, compared sensation scoring before and after treatment within a given treatment group. There were no between-group comparisons. Because of the erroneous statistical calculations, no conclusions about monofilament sensitivity from this very small study (n = 18) can be drawn. The calculations for the Michigan Neuropathy Scoring Instrument (MNSI) questionnaire and the MNSI physical exam similarly lacked between group-comparisons. MNSI-questionnaire scores decreased for both treatment groups of less severely affected patients. MNSI-foot exam scores did not change for any of the patients. The visual analogue pain scores also reportedly improved, but calculations were done only for the entire patient population, and the authors did not address how scoring could be interpreted if each patient contemporaneously received both sham and active treatment.

The studies by Clifft and Zinman et al. highlight the importance of contemporaneous placebo controls with sham treatments and blinding of all parties. In the former trial by Clifft et al., there was a statistically, although biologically questionable, significant increase in the number of sensate areas for the patients randomized to the active treatment group, + 0.37 sites, and patients randomized to the sham treatment group, + 0.57 sites, during the 4 week blinded treatment phase (Clifft). These changes were 39% and 40% of the respective baseline values. Furthermore, sensation improved by another + 0.23 sites in the active treatment group and another + 0.12 sites in the sham treatment group during the withdrawal phase.

In the latter trial by Zinman et al., there was a decrease in the numeric pain rating on the 11 point visual analogue scale for patients randomized to the active treatment group, -1.3 points, and patients randomized to the sham treatment group, -1.5 points, during the 2 week initial sham treatment run-in period. These changes were greater than the subsequent change in the active treatment group over 4 weeks, -1.1 points. These results suggest that there is a major placebo effect in the studies of infrared therapy. Such placebo effects preclude confident interpretation of the many studies in which patients served as their own controls.

4. MCAC

A Medicare Coverage Advisory Committee (MCAC) meeting was not convened on this issue.

5. Evidence Based Guidelines

We searched the National Guideline Clearinghouse (http://www.guideline.gov/) for published guidelines on infrared therapy for the conditions relevant to this NCD. One guideline was found.

> Association for the Advancement of Wound Care (AAWC).
> Summary algorithm for venous ulcer care with annotations of available evidence. 2005. 25 p.
>
> > Grading of other modalities to apply if conservative therapy does not work in 30 days:
> > Laser: C (lowest category for recommendation)
> > Infrared (IR) stimulation (e.g.) monochromatic: C (lowest category for recommendation).
> > http://www.guideline.gov/summary/summary.aspx?doc_id=7109&nbr=004280&string=infrared.
> > (Accessed 6/5/06)

We also searched for guidelines on diabetes, neuropathy, and wound/ulcer treatment. Despite finding many guidelines on these conditions, none (aside from the AAWC above) had a recommendation for infrared therapy. Two from the American Diabetes Association are excerpted below.

> *American Diabetes Association:*
> Consensus Development Conference on Diabetic Foot Wound Care. April 1999. Boston, MA. (Adv Wound Care. 1999;12:353-61, Diabetes Care. 1999;22:1354-1360, J Am Podiatr Med Assoc. 1999;89:475-83.)
>
> "…New technologies include growth factors, living skin equivalents, electrical stimulation, cold laser, and heat. Becaplermin (recombinant platelet-derived growth factor) for the topical treatment of diabetic foot ulcers shows modest benefit if used with adequate off-loading, debridement, and control of infection. Becaplermin is not a substitute for comprehensive wound care. The efficacy of other modalities has not been established or is currently under investigation."
>
> "…New therapeutic modalities "should be evaluated in a consistent and rigorous manner and show substantial evidence of efficacy before being adopted. Evaluation by randomized controlled trials is the gold standard for new therapies. In designing such trials, sufficient numbers of patients must be enrolled to overcome patient variability and obtain adequate statistical power."
>
> *American Diabetes Association:*
> *Consensus statement on diabetic neuropathy (1988)* (Diabetes Care. 1988;11:592-597.)
> *Statement about diabetic neuropathies (2005) (*Diabetes Care. 2005;28:956-962.)
>
> "…The DCCT (Diabetes Control and Complications Trial) has shown definitively that in type 1 diabetic patients, the risk of DPN and autonomic neuropathy can be reduced with improved blood glucose control. Although data from a small number of trials are much less strong for type 2 diabetic patients, DCCT data and data from epidemiologic studies (including studies of type2 patients) strongly suggest that optimal blood glucose control helps to prevent DPN and autonomic neuropathy in both type 1and type 2 diabetic patients. There have been no definitely positive prevention studies of other risk factor modifications for DPN, but the improvement of lipid and blood pressure indexes, and the avoidance of cigarette smoking and excess alcohol consumption, are already recommended for the prevention of other complications of diabetes. The first step in management of patients with DPN should be to aim for stable and optimal

glycemic control."

"...Although controlled trial evidence is lacking, several observational studies suggest that neuropathic symptoms improve not only with optimization of control but also with the avoidance of extreme blood glucose fluctuations. Many patients will require pharmacological treatment for painful symptoms: several agents have efficacy confirmed in published randomized controlled trials, although with the exception of Duloxetine and Pregabalin, none of the others is specifically licensed for the management of painful DPN…".

European Association for the Study of Diabetes; Neurodiabetes Executive Committee Consensus guidelines for diagnosis and management (1998) (Diabetes Metab. 1998;24 Suppl 3:55-65.)

No discussion of infrared therapy.

Association of Francophones for the Study of Diabetes and Diabetic Complications Consensus document on peripheral neuropathy (1997) (Available at: http://www.alfediam.org/members/recommendations/alfediam-neuropathie.asp) (Accessed 3/6/06)

No discussion of infrared therapy.

6. Professional Society Position Statements

CMS did not receive national professional society position statements outside of the public comment process. CMS received written comments from the American Society for Laser Medicine and Surgery (ASLMS) and the North American Association for Laser Therapy (NAALT). The NAALT noted that infrared therapy is a form of phototherapy and that the term, monochromatic infrared energy (MIRE), is not widely used in the literature. Both groups expressed concern that the NCD would limit coverage for infrared devices other than Anodyne. Neither organization provided evidence based guidelines or practice recommendations on the use of infrared therapy for wounds/ulcers or peripheral neuropathy.

7. Expert Opinion

CMS solicited and received an expert opinion from Jeffrey Basford, M.D., Ph.D. and Gail Reiber, M.P.H., Ph.D. Dr. Basford is a board certified physiatrist and has also trained as a graduate level physicist. He is the recipient of extensive extramural funding for laser research. Dr. Reiber is career scientist with the Veterans Administration with research experience in the area of the diabetic foot and the management of diabetic complications resulting in amputation. She served in the working groups that prepared a technical assessment and a position statement on the diabetic foot for the American Diabetes Association. Their comments, excerpted below, are reproduced in their entirety in Appendix D.

Jeffery Basford, M.D., Ph.D. (Professor, Mayo Clinic)

"I believe that most people accept that light produces effects at the level of cellular function that are dependent on wavelength and are not the result of heating. Unfortunately, translation of these results to animals and humans has been difficult with many experiments showing benefits and others showing little or no effect. Initial research typically involved low power helium-neon lasers as noted above as well as other devices such as argon or krypton lasers. However, once superluminous, and laser diodes became available, efforts focused on red and IR radiation due to cost, ease of use, improved tissue penetration, and report of benefits. Soft tissue injuries, wounds, and pain have consistently been the center of experimental and research interest.

Research in the U.S. began in the late 1970s and in 1985, and FDA. Pre-Market Approval (PMA) Review Panel reviewed the effects of helium-neon laser irradiation on rheumatoid arthritis. The panel concluded that evidence of efficacy was too limited to permit a recommendation of acceptance. I performed my last published review in 1995 and concluded that the field had exciting possibilities, but that clinical benefits had yet to be established. Research has continued subsequently with numerous investigators finding benefits; again with the most marked finding at the basic science level and with difficulty obtaining overwhelming evidence of clinical benefits. Many in the field may consider me conservative in this assessment. However, I reviewed the Cochrane Database…and confirmed that members of this collaboration find little or no support for the use of light therapy for osteoarthritis, lower extremity venous ulcers, or tuberculosis and only weak support for the treatment of rheumatoid arthritis. The overall assessment is that better designed, controlled, and powered studies are needed…"

Dr. Basford recommended the World Association of Laser Therapy website (http://www.walt.nu) as a reference.

Gail Reiber, M.P.H., Ph.D. (Professor, University of Washington)

"We reviewed the published evidence on infrared therapy and diabetic peripheral neuropathy. Uncontrolled studies show a beneficial effect from monochromatic infrared energy on peripheral sensation.[1-3] However, without a suitable placebo control group, inferences cannot be made on the device efficacy. Two randomized, double-blind, placebo-controlled trials came to differing conclusions. The first by Leonard, et al.[4] was designed with the primary outcome being change in sensitivity to the 5.07 monofilament. There was no a priori hypothesis regarding differences between 5.07 and 6.65 monofilaments. Nor was there a priori specification of subject stratification based on initial monofilament response. The randomized treatment protocol delivered ATS Model 480, Anodyne Therapy System (ATS) three times per week for 40 minutes for two weeks. Then unfortunately the randomized design collapsed and all subjects received ATS treatment for an additional two weeks. The controlled data for the first two weeks is presented in two strata, and the intent-to-treat analysis is not clearly presented. Leonard and colleagues report important findings in the paper for the two-week treatment, including decreased pain, and improved balance. Nothing can be stated for the interval for which there are no control data. Thus we can say little about efficacy.

The Clifft study[5] randomized 39 subjects with diabetic peripheral neuropathy of varying severity to an eight-week of study of monochromatic infrared energy (MIRE) three times per week for eight weeks with monofilament measures at baseline, 4 and 8 weeks. This well-designed study found no difference between intervention and control subjects in sensitivity to the 5.05 monofilament at the trial conclusion.

Diabetic peripheral neuropathy represents neuronal death. Nerve regeneration down the axonal tube is possible, but this reinnervation takes from months to years. Two to eight weeks is not sufficient for this process to occur. Thus additional studies on this potential therapy are needed that are more specific in terms of therapeutic interval, dose, placement of therapy pads, and threshold levels. Subjects should be more homogenous in terms of type of diabetes and severity of neuropathy.

8. Public Comments

Initial public comment period

During the initial comment period, CMS received a total of 1315 comments. Of the 1315 comments, 1077 comments were posted to our website during the public comment period. CMS received the remaining 238 comments through the mail or by e-mail, and scanned and subsequently posted them to the CMS website. Many of the comments from patients, individuals working in the health care setting, and clinicians were in response to a form letter sent by Anodyne® requesting comments be submitted with regards to their device. Comments that were submitted directly to Anodyne® were forwarded to CMS by Anodyne®. As we note in Appendix A, reports of individual cases usually do not carry as much evidentiary weight as methodologically rigorous clinical trials. This is particularly important when considering conditions where the natural history includes waxing and waning of symptoms, a placebo effect is likely to be present, or where symptom relief may be associated with worsening rather than improvement of the underlying medical condition. Thus, the enthusiasm of individual commenters must be tempered by prudent concern about these confounding factors. All three of these factors are relevant in the consideration of neuropathic pain, where symptoms commonly come and go over time, placebo treatment is associated with subjective symptom improvement, and progression of nerve damage may be associated with pain improvement.

All but 3 of the 1315 comments supported the use of infrared therapy. Seven hundred ninety-four were from patients who have used infrared therapy at home and/or as part of therapy and had success and encouraged CMS to cover this benefit. Five of the 794 commenters identified themselves as clinicians who personally used infrared therapy and believe it should be covered. One hundred sixty-four comments were from individuals who worked in the health care setting such as a home health agency, rehabilitation center, hospital, or skilled nursing facility, who had themselves used or seen infrared therapy work for patients and supported coverage. Three hundred twenty-four comments were from clinicians, including certified occupational therapy assistants, podiatrists, physicians, nurses, occupational therapists, and physical therapists, who used infrared therapy on patients and noted positive outcomes

Of the 1315 comments, 6 individuals identified themselves as employees of Anodyne® who believe infrared therapy should be covered. One commenter was a Durable Medical Equipment supplier of Anodyne® and believes the therapy should be covered based on their experience of providing this device to patients. Fifteen commenters who worked in the health care setting mentioned another infrared therapy device in addition to or separately from the Anodyne® device. All 15 commenters wrote of successful outcomes and encouraged us to cover infrared therapy. Five individuals submitted case reports, abstracts or articles as references. None of this information, however, was published. One commenter stated disbelief that CMS could non-cover this infrared therapy because a local Medicare contractor currently covered this therapy.

One individual mentioned they were in the process of researching cold laser therapy with exercise and has seen improvements in patients thus far. Another individual, who was an associate professor, had conducted a preliminary research on Anodyne® and its impact on patients with osteoarthritis. The individual indicated that a study is needed in order to establish efficacy of Anodyne® as a non-pharmaceutical intervention.

Second public comment period

During the second public comment period CMS received 4,130 comments. Many of these were submitted via Anodyne®, either by company employees directly or via company employees who sent in summaries of telephone calls apparently made by the company to generate comments from Anodyne® users. Many comments contained identical language, including misspellings. Other comments appeared to be in response to a letter sent by Anodyne because they consisted of a sequence of similar short answers responding to the questions posed by the letter. Yet another series of comments resulted from a survey of Anodyne® users conducted by a physical therapy office. The results were forwarded to Anodyne®. We also received comments from practitioners and distributors outside of the United States, including Japan, the Peoples Republic of China, Dubai, and the United Arab Emirates. Most comments supported coverage of infrared therapy.

Comment: Most comments were directed at the Anodyne Therapy System®. Most commenters reported positive personal experiences. These commenters were patients, patients' family members, or therapists providing services with the device. A small number of commenters reported negative or equivocal personal experiences with an Anodyne® device, either as patients or patients' family members. One provided specific anecdotal comment regarding the therapeutic regimen: minimal benefits were accrued only after 3 to 4 treatments per week; but 5 or more treatments per week did not confer additional benefit.

Response: The medical conditions that are discussed in this decision memorandum are indeed complex, though they may to the lay person appear to be straightforward. Sensory neuropathy is not a single condition; it is a family of different conditions, each with its own underlying pathophysiology and natural history. Skin wounds and ulcers are similarly varied in their underlying pathophysiology and natural history. Thus we have had to pay scrupulous attention to the methodologies which have been used to generate the evidence that we have reviewed, including public comments.

Rigorous clinical trials are particularly important when considering conditions where the natural history includes waxing and waning of symptoms, a placebo effect is likely to be present, or where symptom relief may be associated with worsening rather than improvement of the underlying medical condition. The lack of attention to these confounding factors diminishes the weight of individual commenter experiences with infrared therapy for these conditions. As noted in Appendix A, even individual case reports published in peer-reviewed medical literature are generally given less evidentiary weight than methodologically rigorous studies.

Comment: One commenter from an overseas manufacturer of laser products for lymphoedema and one athletic trainer who is a certified laser specialist expressed concern that laser technology be distinguished from light emitting diode technology.

Response: The technical differences between the light sources are discussed in the historical background section of the memorandum. The search criteria for published clinical trials were broad and sought to include studies using infrared from a variety of sources. The analysis sought to determine whether the variable properties of light emission as well as wavelength contributed to efficacy or lack of efficacy. See Appendix E and Background section for further detail.

Comment: Two commenters from professional societies (American Society for Laser Medicine and Surgery [ASLMS] and the North American Association for Light Therapy [NAALT]) noted that CMS did not include all infrared pre-clinical and physiologic studies in our memorandum.

Response: In general, when making national coverage determinations, our analysis focuses on clinical trials with validated clinical outcomes. *In vitro* studies, animal studies, and early phase I-II studies may provide mechanistic explanations for the clinical outcomes, but do not provide adequate evidence on patient-centered health outcomes and, thus, may not be as persuasive as the results from substantive clinical trials. There is no consensus on a mechanistic pathway for infrared therapy. Appendix E included mechanistic studies delineating some of the putative pathways pertinent to wound and nerve healing. One of the commenters did not provide any additional clinical studies for review. The other included 21 pre-clinical citations and 1 incomplete, non-Medline abstract citation. Data from this study of six patients treated with a combination of infrared and red light or placebo have been included in the evidence tables (Lanzafame).

Comment: Multiple commenters requested review of work by Dr. Whelan.

Response: Numerous pre-clinical studies by this investigator and his collaborators were reviewed. One, by Wong-Riley et al. was cited in the mechanistic section (Appendix E) (Wong-Riley). No sanctioned clinical trials appear to have been conducted by Whelan et al. on SEALs or other Navy personnel (Whelan). Data from a non-Medline abstract for a clinical trial of 6 patients with "diabetic venous stasis ulcers" treated with combination infrared and red light therapy on which Dr. Whelan was a co-author were included in the evidence tables (Lanzafame).

Comment: A physical therapist suggested review of meta-analyses by Enwemeka and colleagues. Incomplete citations were provided (Enwemeka, Woodruff).

Response: The studies did not identify new clinical trials that should have been assessed in the memorandum. The meta-analyses were limited because of their inclusion of heterogeneous studies, including animal studies. In addition, although the analyses delineated inclusion and exclusion criteria, they did not clearly identify the studies that were included in the analysis.

Comment: Another physical therapist suggested review of an article in Gerinotes, a non-Medline American Physical Therapy Association newsletter, in which case series data for 3 patients were presented (Pappas).

Response: These data were analyzed and included in the evidence tables.

Comment: The Anodyne® company submitted "The Role of Monochromatic Infrared Photo Energy (MIRE) in the Treatment of Diabetic Peripheral Neuropathy" prepared by The Weinberg Group, dated June 12, 2006 and labeled "Prepared for Anodyne Therapy Systems LLC." This document reviewed some of the existing published literature on infrared therapy and offered a conclusion that supported the Anodyne Therapy System.

Response: This document is not a systematic review with pre-specified inclusion criteria, pre-specified criteria for rating the strength of the data, and critical analysis of statistical methods. The manuscript did not identify new published studies for CMS review. The analysis did not address the incorrect statistical methods that were the basis of the positive conclusions in the Leonard study (Leonard).The unpublished document has not undergone peer review for inclusion into the medical literature. After reviewing the primary data as individual studies and in the aggregate, CMS believes that CMS' conclusion is more consistent with the evidence than the commenters' conclusion.

Comment: Some commenters asked CMS to provide limited coverage under the Coverage with Evidence Development (CED) paradigm. Specifically, we were asked to provide coverage to Medicare beneficiaries who would be enrolled in a registry.

Response: Coverage with Appropriateness Determination (CAD) cannot be provided under Coverage with Evidence Development (CED) in the absence of an affirmative finding of reasonable and necessary. In this decision, CMS has not determined that infrared therapy is reasonable and necessary for the treatment of diabetic and/or non-diabetic peripheral neuropathy, wounds and/or ulcers of skin and/or subcutaneous tissues in Medicare beneficiaries. (Information from the guidance document on CAD and CED may be found athttp://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8.)

Comment: In a letter dated August 24, 2006, the Anodyne® company stated that CMS Administrator Mark McClellan, during August 21, 2006 public comments at the Montana 2006 Quality Living for Montana Seniors Conference, said "that he is supportive of a revision to the proposed decision memorandum based on this evidence, perhaps with the inclusion of a requirement for further evidence development…".

Response: We have no record of that particular statement. A review of copies of the CMS Administrator's prepared slides, as well as final draft comments for the Montana conference, did not reveal discussion of infrared therapy, the currently open national coverage analysis, Anodyne®, or Coverage with Evidence Development (CED).

Comment: One commenter claimed that the pharmaceutical industry was behind the proposed noncoverage decision.

Response: Pertaining to this national coverage analysis, CMS has not received any communication recognized as coming from the pharmaceutical industry or their representatives. CMS staff have not been apprised of their position(s) on this issue.

Comment: Several commenters including the presidents of ASLMS and NAALT suggested that the scope of the decision be modified to specifically exclude coverage for Anodyne, but not other devices.

Response: All available published evidence for infrared therapy and the delineated indications was reviewed. The data were not limited to the Anodyne® devices. The data do not support differentiation of the Anodyne® devices from other forms of infrared therapy.

Comment: Several commenters noted that most burn reports were associated with Anodyne® devices.

Response: The FDA MAUDE database was searched by year and product class. Whether the predominance of adverse events for Anodyne® reflects market share or specific features of its products is unknown.

Comment: One commenter expressed concern that 1) there was no information on testing and maintenance of his Anodyne® unit, 2) one could not tell if all LED units were functional, 3) the entire system had to be disconnected if one unit was inoperable, 4) cleaning resulted in electrical shorting, and 5) a timer was lacking. The commenter did not report an actual burn.

Response: Consumer concerns about particular products should be addressed to the manufacturer or the FDA or other Federal agencies that have oversight of the products in question

Comment: Some commenters noted that diabetes care is expensive, and suggested that infrared was cost effective.

Response: CMS is aware of the costs of diabetes care. CMS does not consider cost in making NCDs. This policy is explicitly noted in a guidance document that is publicly available at the URL below.

> http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=6
>
> "Cost effectiveness is not a factor CMS considers in making NCDs. In other words, the cost of a particular technology is not relevant in the determination of whether the technology improves health outcomes or should be covered for the Medicare population through an NCD."

CMS is also aware that the therapeutic options for some aspects of diabetes care are quite limited and that these are areas of active research. CMS is interested in identifying and providing coverage for effective treatment modalities for diabetes and its complications.

Comment: Some commenters suggested that toenail growth, hair growth, reduced swelling, wound healing, or return of sensation cannot be due to placebo effects.

Response: We disagree. These findings may wax and wane in the natural course of the conditions that are the focus of this decision. In the absence of rigorous systematic assessment using validated measurement techniques, we cannot be confident that there is a positive effect not due to placebo.

Comment: Some commenters reported that infrared therapy is used by the Armed Forces.

Response: The coverage decisions made by CMS reflect the available evidence for the Medicare beneficiary population. CMS does not make coverage determinations for other governmental agencies and other population groups. Nor are decisions of other agencies, that may be made under different statutory provisions, controlling for Medicare purposes.

Comment: One commenter stated that the benefit of the device required three to four times a week use, and that use five or more time a week had no incremental benefit.

Response: As we have noted above, reports of personal experience do not carry the evidentiary weight of robust clinical trials.

Comment: Several commenters noted a high school science project that they said supported infrared therapy. The project itself was not submitted for review.

Response: We did not review the project. High school science projects are not generally included in the body of peer reviewed published medical literature that is generally accessible.

Comment: Several commenters asked us to review specific articles and/or abstracts and/or reports. Generally the comments did not include actual copies of the material.

Response: In several cases we had already reviewed the materials in the proposed decision memorandum, but the commenters apparently had missed the relevant text. In other cases we tried to obtain the materials for review from online or other sources. Our consideration of these materials are discussed elsewhere in this decision memorandum.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” §1862(a) (1) (A). This section presents the agency’s evaluation of the evidence considered and conclusions reached for the assessment question:

Peripheral neuropathy and skin ulcers and wounds are complex conditions with multiple etiologies that may coexist in individual patients. As noted above, the symptoms of peripheral neuropathy may wax and wane spontaneously. Paradoxically, pain relief may accompany a worsening of the underlying condition of the nerve. In addition, pain relief is subject to a placebo effect that requires appropriate blinding and control. This may be a smaller concern for skin ulcers and wounds, which are more amenable to objective measurement and photographic documentation.

Although there have been many published reports of clinical trials of infrared therapies for the conditions relevant to this NCD, most have methodologic shortcomings that to varying degree weaken the confidence that can reasonably be accorded to many of their authors’ stated conclusions. In many instances the conclusions offered by the authors cannot be accepted at face value, and we are thus unable to confidently reject alternative explanations for the same results. In some instances the trial methodology is so inadequate that we can reach no robust conclusion about the trial results. External technology reviews and evidence based guideline have, when infrared therapy is mentioned at all, given it low ratings.

Questions:

> *1. Is the evidence sufficient to determine that infrared therapy improves health outcomes in Medicare beneficiaries with skin wounds or skin ulcers?*

2. Is the evidence sufficient to determine that infrared therapy improves health outcomes in Medicare beneficiaries with peripheral sensory neuropathy?

3. If the answer to Question 1 and/or Question 2 above is affirmative, what characteristics of the patient, the disease, or the treatment reliably predict a favorable health outcome?

Skin wounds or skin ulcers and peripheral neuropathy may impact a patient in many ways, including causing pain or numbness, soft tissue destruction, malodorous drainage, weakness or difficulty with balance and walking, and providing a portal for infection of deeper structures. These are generally chronic conditions marked either by inexorable progression or waxing and waning over time. In some cases, amputation of the affected body part is the definitive treatment. Thus, we believe that the broad questions above are appropriately addressed by considering specific subsidiary questions.

What effect does infrared therapy have on the percent of wounds or ulcers with complete closure? Does infrared therapy accelerate the time to complete closure, and increase the percent of wounds or ulcers that remain closed 6 months after complete closure? Does infrared therapy reduce the amputation rate for non-healing wounds or ulcers?

Does infrared therapy reduce neuropathic pain, the rate of new neuropathic ulcers, or the fracture rate (wrist, hip) from falls due to insensate feet?

Are reported response rates related to the underlying etiology of the wound or neuropathy? Are the reported response rates with infrared light therapy better than those associated with appropriate usual medical treatment of the underlying disorder?

What are the specific features of infrared light therapy devices and treatment regimens that may contribute to any reported efficacy in Medicare beneficiaries? Are all devices and regimens equally efficacious? Does infrared therapy have a sustained effect or is continuous therapy required?

The available studies do not support use of infrared therapy for any type of wound, ulcer, or peripheral sensory neuropathy in any population. Results from the small randomized studies did not reveal differences between infrared and placebo treated patients. There was a significant placebo effect. Many of the studies lacked definitive clinical endpoints of importance to the Medicare population. The studies were not structured to assess durability of effect. The many variables in the assorted devices and treatment regimens suggest the need for additional phase I-II studies.

The studies by Clifft and Zinman et al. highlight the importance of contemporaneous placebo controls with sham treatments and blinding of all parties (Clifft, Zinman). Improvements in sensation for both treatment arms during the sham treatment run-in period and improvement in the numeric pain rating scale in the blinded sham treatment arm revealed a major placebo effect in the studies of infrared therapy. Such placebo effects preclude confident interpretation of the many studies in which patients served as their own controls.

Most of these controlled studies were not conducted using hard clinical endpoints of real interest to Medicare such as amputation rates in neuropathy trials and the time-to-complete healing and the percent of patients with total closure in wound trials. The use of surrogate or intermediate rather than hard endpoints may be reasonable alternatives when validated surrogate or intermediate endpoints exist and when the natural course of the disease is such that the passage of time between the intervention and the expected clinical outcome is so long that a clinical trial could not practically be accomplished. CMS does not believe that there are generally accepted validated surrogate or intermediate endpoints for the questions posed in this decision memorandum. CMS believes that assessment of complete wound healing is an endpoint that is achievable within a reasonable clinical trial time frame, and that the presence or absence of complete wound healing is more important than changes in the size of the wound. Only the small study conducted by Malm et al. utilized the portion of patients with complete wound closure as an endpoint.

The use of surrogate endpoints introduced problems linked to the test modalities. For example, the monofilament can be utilitarian in the clinical setting (Abbott, Boyko, Jirkovska, Olmos, Rith-Najarian, Saltzman), but has not been fully validated for use in intervention trials (Jeng). The tool is subject to both operator and device error. The original horsehair and later nylon monofilaments were carefully weighted and calibrated (Bell-Krotoski 1987, 1995, 1997, Birke, Omer, Weinstein). The instruments used for screening in clinical practice, however, are typically disposable and imprecise tools (Booth, McGill 1998, 1999). The monofilament is intended to assess pressure sensation. The filament must be applied at a 90 degree angle to the skin and enough weight applied to just bend the filament. Application of too much weight on the filament can result in activation of fine touch sensors. Application that is too brisk or with a filament with a roughly cut edge can result in activation of pain sensors. A filament that is longer or shorter than the calibrated instrument will require a different amount of weight to initiate filament bending (McGill 1998, 1999). The levels of buckling force also can be affected by humidity (Brydson) as well as the number of compressions and the duration of the subsequent recovery period (McGill 1998, 1999).

The monofilament test reproducibility between examiners is limited (kappa= 0.59 [95% confidence interval 0.48-0.71]) and differs by anatomic location (Smieja). Serial reproducibility of the monofilament testing over time is poorly characterized; its use proliferated after utilization in cross-sectional surveillance or cohort studies linked skin ulcer risk with impaired monofilament sensation (Abbott, Boyko, Jirkovska, Olmos, Rith-Najarian, Saltzman). The exact number and location of sites to be tested is also still debated (McGill 1999). Finally, sensory testing was not done with an algorithm for repeated measures of a given neurologic parameter, (continuous or categorical) so that intrapatient variation could be established (Dyck 1990, 1993, Holewski, Salzman). Although the investigators of the most rigorous trial of hypoesthesia, Clifft et al., used a series calibrated monofilaments and described monofilament positioning in the methods, they did not address the other short-comings of the measurement tool and did not employ any other assessments of sensory dysfunction (Clifft). Of note, the investigators of the most rigorous trial of neuropathic pain, Zinman et al., reported no improvement in either the primary endpoint or the secondary endpoints (monofilament testing and quantitative sensory testing [vibration, temperature]), but did not provide a complete description of the methodology or results (Zinman).

Various methods were used to assess serial changes in wound area such as wound perimeter tracings with the area calculated with a mechanical drafting planimeter, digital planimetry or wound photographs with the area calculated by planimeter, and digital planimetry. Unfortunately these methods are not well validated in these settings (Lagan 2000, Majeske, Thawer 2002, van Zuijlen). The addition of a third dimension (depth) to determine wound or ulcer volume further compounds measurement uncertainty.

There are conflicting data as to whether digitalization provides more reproducible measurements (Lagan 2000, Majeske, Thawer 2002). Although photography may improve accuracy, it appears to be less accurate in the measurement wounds in curved areas (van Zuijlen). Multiple measurements may improve accuracy (Thawer 2002). Of the 6 controlled trials for wounds, only Lagan et al. delineated repeated area measurements (n = 3) at each time point (Lagan 2001).

The studies also lacked assessment of the long-term durability of any treatment effect after treatment cessation, using either hard clinical parameters such as amputation rates or skin ulcer recurrence at 3 to 6 months post closure or surrogate endpoints such as neuro-sensory function tests (Faglia, Fassiadis, Ghauri, Hartemann-Heurtier, Pound, Wissing). None of the controlled studies for wound healing had a post treatment assessments to evaluate the integrity of wound closure. Only 2 of the neuropathy studies had post-treatment assessments. The withdrawal periods were limited to 2 and 4 weeks respectively in the studies by Zinman and Clifft et al.

A further limitation of the controlled studies was small sample size. The trials assessing wounds included 9 patients (Lagan 2001), 16 patients (Lucas 2000), 18 patients (Palmgren), 46 patients (Malm), and 86 patients (Lucas 2003) in 2 treatment arms as well as 65 patients (Franek) in 3 treatment arms. The trials evaluating peripheral neuropathy included 27 patients (Leonard), 43 patients (Cliff t), and 50 patients (Zinman).

Studies of this topic are complicated by many variables in the treatment devices and treatment regimens. Basic data on the type of light to use are missing. It is not known whether red light or infrared light is optimal. It is not known whether monochromatic light is more advantageous than continuous polychromatic light or a combination of wavelengths. It is not known whether benefits are limited to use of coherent light. It is not known whether the pulsed delivery of monochromatic light confers advantage over non-pulsed light and, if so, what the length of the duty cycle should be. The investigators did not construct trials to assess any of these variables in treatment devices. Basic dose-ranging data are missing. The optimal energy density, single-dose duration, dose interval, and cumulative dose have not been established. Basic data on the interaction between diseased tissues and light is missing. It is not known whether assorted cutaneous wound and nerve tissues have the same response to light. Additional exploratory work would further clarify the role of these variables. Only when basic efficacy has been established can investigators determine through additional studies which populations, if any, might benefit from experimental light therapy. Head-to-head trials will reveal whether adverse events such as burns are attributable to the technology as a whole or to specific devices (Anwar, Gul, Harley, Health Devices, Khan, Madura,Takac).

The published medical literature we reviewed may be considered to fall in two broad categories. The first contains a large number of studies purporting to support infrared therapy, but which are hampered by significant methodological flaws that undermine their conclusions. Considered as a class, they fail to provide evidence that infrared therapy is reasonable and necessary for the clinical conditions discussed in this decision memorandum. The second comprises a very small number of studies that are methodologically stronger. We believe they provide evidence that infrared therapy is not reasonable and necessary for the clinical conditions discussed in this decision memorandum. Thus, in sum, we conclude that the currently available published medical literature does not support infrared therapy.

We are aware currently of two large clinical trials in progress on infrared therapy. Because they have not yet been completed or published in the medical literature, we cannot review them in this decision memorandum.

CMS received a large number of public comments regarding the proposed decision. Readers of this decision memorandum may wonder why the large number of comments opposing the proposed decision did not lead us to disregard the inconclusive or negative published medical literature in order to reach a positive final determination. Although the published medical literature on infrared therapy has its deficiencies, it is methodologically more rigorous than anecdotal case reports.

Public comments can offer a perspective on the potential impact of CMS decisions. Public comments can call our attention to medical literature that may provide useful evidence. Public comments that offer alternative interpretations of the evidence can prompt us to re-examine our own conclusions. Public comments can also provide useful information on how an item or service is used in the community.

In summary, the negative outcomes in the controlled studies do not support use of infrared therapy for the treatment of any type of wound, ulcer or peripheral sensory neuropathy or management of the symptoms associated with any type of wound, ulcer or peripheral sensory neuropathy. In addition, infrared therapy devices have not been approved by the FDA for the treatment of diabetes, diabetic or non-diabetic neuropathy, skin wounds, or dermal ulcers. There are reports of harms, generally burns, associated with infrared therapy. These reports are particularly worrisome because the population purported to benefit from infrared therapy is already at heightened risk for burns due to loss of protective sensation. CMS received and considered comments favoring coverage from two professional organizations of laser therapy; CMS did not receive any comments from the professional medical and surgical societies more classically associated with the care of wounds, neuropathy, and their underlying medical conditions, e.g., diabetes. The published evidence-based guidelines for these conditions do not include infrared therapy or designate it as ancillary therapy with a minimal evidence base.

IX. Conclusion

CMS has determined that there is sufficient evidence to conclude that the use of infrared devices is not reasonable and necessary for treatment of Medicare beneficiaries for diabetic and non-diabetic peripheral sensory neuropathy, wounds and ulcers, and similar related conditions, including symptoms such as pain arising from these conditions. Therefore, we are issuing the following National Coverage Determination.

The use of infrared and/or near-infrared light and/or heat, including monochromatic infrared energy (MIRE), is not covered for the treatment, including symptoms such as pain arising from these conditions, of diabetic and/or non-diabetic peripheral sensory neuropathy, wounds and/or ulcers of skin and/or subcutaneous tissues in Medicare beneficiaries.

Appendix A

General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be

extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendices B - F

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