



CIGNA MEDICAL COVERAGE POLICY

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

Subject Histamine Desensitization Therapy

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Coverage Policy Number 0436

Table of Contents

Coverage Policy	1
General Background	1
Coding/Billing Information	3
References	3
Policy History.....	5

Hyperlink to Related Coverage Policies

- Acupuncture
- Antimigraine Therapy
- Biofeedback
- Hyperbaric Oxygen Therapy
- Oxygen for Home Use

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

Coverage Policy

CIGNA does not cover intravenous or subcutaneous histamine desensitization therapy for the treatment of any condition because it is considered experimental, investigational or unproven.

General Background

Headaches can be experienced by all age groups, from young children to the elderly. Although the majority of people experience tension-type headaches at some time in their lives, approximately 30 million experience migraine headaches. Smaller percentages of people, by comparison, suffer with other chronic headaches such as cluster headaches or chronic daily headaches. There is no sure diagnostic test available to differentiate headache types. The headache condition can progress over time in frequency, severity, and debilitation. Each sufferer can be different and may require a detailed evaluation and individualized treatment plan; the more frequent or prolonged attacks often necessitate a more comprehensive treatment plan (Gallagher, 2007).

There are two elements of headache treatment: abortive treatment, directed at attacks once they have begun, and prophylactic treatment, directed at preventing or reducing the frequency of attacks. In general, the abortive approach is for patients who suffer infrequent attacks and for those who experience breakthrough attacks while on prophylactic therapy. Prophylactic therapy is typically instituted when headaches are frequent, unresponsive to abortive medication, or when there is a contraindication to abortive treatment. Headache treatment can include nonpharmacologic measures such as physical exercise, stretching, stress avoidance, relaxation

exercises, biofeedback, manipulation, massage, or cold/warm packs. Pharmacologic therapies can include a wide array of medicaments from over-the-counter (OTC) drugs to prescription drugs such as triptans, other vasoconstrictors, β -blockers, antiepileptic agents, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, muscle relaxants, anxiolytics, and others. Histamine is thought to play a role in the development of pain and has been shown to induce migraine, prompting investigation of histamine desensitization for prevention of severe migraine or treatment of chronic cluster headache unresponsive to other medications (Gallagher, 2007; Hayes, 2007).

Desensitization is a form of immunotherapy where the patient is gradually given progressively larger doses of the allergen in question, in this case, histamine. Histamine is the primary toxin released by basophils and tissue mast cells during an allergic reaction. Other causes of histamine release include a reaction to drugs, a physical insult, stress, or spontaneous basophil release. Histamine desensitization was popular in the 1940s and 1950s, although the treatment is rarely used at this time. There have been anecdotal reports regarding the usefulness of histamine therapy. Patients were treated with subcutaneous and intravenous injections based on the contention that metabolic derangement of histamine played an important role in producing cluster headaches. Histamine therapy has also been proposed for vertigo, cancer, Bell's palsy, vestibular disorders and multiple sclerosis. Increasing doses of histamine are generally administered via subcutaneous injections or intravenous infusion over a period of approximately 1–3 months. Patients receiving intravenous infusions are usually hospitalized for approximately 10–30 days. Patients receiving subcutaneous injections are generally treated in an outpatient setting (Hayes, 2007; Gallagher, 2007; Sargeant and Blanda, 2007; Biondi, et al., 2004; Freitag, 2004; Gillison, et al., 2000; King, 1999).

U.S. Food and Drug Administration (FDA)

The Center for Biologics Evaluation and Research (CBER) regulates allergenic products. There are currently two types of allergenic products licensed for use: allergen patch tests and allergenic extracts (FDA, 2007a). There are currently three licensed histamine products listed in the FDA National Drug Code Directory; two products are intradermal preparations (FDA, 2007b).

Literature Review

Millán-Guerrero et al. (2007) conducted a 12-week double-blind, placebo-controlled clinical trial to evaluate the therapeutic potential of subcutaneous administration of histamine (1–10 ng twice a week; n=46) in migraine prophylaxis, compared with oral administration of sodium valproate (500 mg daily dose; n=46). The patients were diagnosed with recurrent migraine unresponsive to available abortive and/or prophylactic agents. The variables studied were headache intensity, frequency, duration, analgesic intake and migraine disability assessment (MIDAS). The data collected during the 4th, 8th and 12th weeks of treatment revealed that histamine caused a significantly greater reduction ($p < 0.001$) in intensity and duration of migraine attacks as well as in analgesic intake. No difference was detected in the frequency of attacks or in MIDAS. Eleven patients left the study because they were not satisfied with the speed of the results. Six of these patients stopped taking sodium valproate during the first weeks because of the side effects. Five patients from the histamine group abandoned the study even though they presented with no side effects. The reported limitations of this study are the small sample size, and the patients were recruited from the general population and not from a headache specialty clinic.

Millán-Guerrero et al. (2006) conducted a double-blind, placebo-controlled Phase III clinical trial which evaluated the efficacy of $N\alpha$ -methylhistamine in patients with recurrent migraine unresponsive to traditional abortive or prophylactic therapies. In this 12-week clinical trial, the efficacy of subcutaneous administration of $N\alpha$ -methylhistamine 1–3 ng twice a week against placebo was studied, evaluating the outcome of headache intensity, frequency, duration, and analgesic intake. Comparison between the groups treated with placebo (n=30) and $N\alpha$ -methylhistamine (n=30), on data collected for the 4th, 8th and 12th weeks of treatment, revealed that compared to placebo, $N\alpha$ -methylhistamine exerted a significant ($p < 0.0001$) reduction in intensity, frequency, and duration of migraine attacks, as well as the use of analgesics. No significant ($p > 0.05$) adverse experiences or side effects developed in either group. Patients in both groups reported transitory burning and itching at the injection site. Three $N\alpha$ -methylhistamine and two placebo patients withdrew because of a lack of efficacy. Patients were reported to be free of migraine or had significant relief of symptoms for a period ranging from 6–12 months following the study.

King (1999) conducted a retrospective office study of 100 randomly selected patients with headache and/or vertigo. Low-dose histamine appeared to be helpful in 70% of the patients and some value in 10% of patients.

The author reported that 20% of the patients did not improve within two months on the treatment and were switched to a different therapy.

In 2007, Hayes published a Hayes™ Technology Brief on histamine desensitization therapy for prophylaxis against intractable migraine or chronic cluster headaches. The authors concluded, “there are very few data on the efficacy of histamine desensitization in the treatment of intractable migraine or cluster headaches. Overall, the evidence suggests that histamine desensitization may be effective in some patients with severe, recurrent migraine headaches that are unresponsive to other medications or treatment; however, the optimal place for this therapy in the migraine or cluster headache treatment algorithm remains to be established. If the results obtained in the randomized controlled trials were to be replicated by another independent group, the results taken together might provide a compelling case for histamine treatment” (Hayes, 2007).

Professional Societies/Organizations

The 2000 evidence-based guideline for treatment of migraine headache developed by the American Academy of Neurology does not mention histamine desensitization therapy as a treatment for migraine (Silberstein, 2000).

Summary

There is a paucity of evidence addressing the safety and efficacy of subcutaneous or intravenous histamine desensitization therapy as a treatment for intractable headaches or any other condition. In addition, effectiveness has not been compared to other established pharmacotherapy. Well-designed randomized clinical trials are needed to address the safety and effectiveness of this treatment.

Coding/Billing Information

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

Covered when medically necessary:

CPT®* Codes	Description
	No specific codes

HCPCS Codes	Description
	No specific codes

ICD-9-CM Diagnosis Codes	Description
	All codes

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

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	2/15/2008	0436	Histamine Desensitization Therapy

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.