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|-------------------------|----|---|--------------------------------|
| <b>Medical Benefit</b>  |    | <b>Effective Date:</b> 01/01/19   | <b>Next Review Date:</b> 11/19 |
| <b>Preauthorization</b> | No | <b>Review Dates:</b> 03/08, 05/09, 01/10, 01/11, 01/12, 01/13, 01/14, 11/14, 11/15, 11/16, 11/17, 11/18 |                                |

***Preauthorization is encouraged for reconstructive services.***

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

| Populations  | Interventions  | Comparators  | Outcomes   |
|--|--|--|--|
| Individuals:<br>• With primary focal hyperhidrosis (i.e., axillary, palmar, plantar, craniofacial) | Interventions of interest are:<br>• Iontophoresis                                    | Comparators of interest are:<br>• Topical antiperspirant<br>• Oral medication<br>• Botulinum toxin | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With primary axillary hyperhidrosis  | Interventions of interest are:<br>• Botulinum toxin type A or B                      | Comparators of interest are:<br>• Topical antiperspirant<br>• Oral medication                      | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With primary palmar hyperhidrosis  | Interventions of interest are:<br>• Botulinum toxin type A or B                      | Comparators of interest are:<br>• Topical antiperspirant<br>• Oral medication                      | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With primary plantar hyperhidrosis   | Interventions of interest are:<br>• Botulinum toxin type A or B                      | Comparators of interest are:<br>• Topical antiperspirant<br>• Oral medication                      | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With primary focal hyperhidrosis (i.e., axillary, palmar, plantar, craniofacial) | Interventions of interest are:<br>• Microwave treatment<br>• Radiofrequency ablation | Comparators of interest are:<br>• Topical antiperspirant<br>• Oral medication<br>• Botulinum toxin | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With primary axillary hyperhidrosis  | Interventions of interest are:<br>• Surgical excision of axillary sweat glands       | Comparators of interest are:<br>• Topical antiperspirant<br>• Oral medication                      | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With primary axillary, palmar, and craniofacial hyperhidrosis                    | Interventions of interest are:<br>• Endoscopic transthoracic                         | Comparators of interest are:<br>• Topical antiperspirant<br>• Oral medication                      | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |

| Populations   | Interventions  | Comparators   | Outcomes   |
|---|--|---|--|
| Individuals:<br>• With primary plantar hyperhidrosis            | Interventions of interest are:<br>• Lumbar sympathectomy               | Comparators of interest are:<br>• Topical antiperspirant<br>• Oral medication | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With severe secondary gustatory hyperhidrosis | Interventions of interest are:<br>• Iontophoresis<br>• Botulinum toxin | Comparators of interest are:<br>• Diet<br>• Topical medications               | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |
| Individuals:<br>• With severe secondary gustatory hyperhidrosis | Interventions of interest are:<br>• Tympanic neurectomy                | Comparators of interest are:<br>• Diet<br>• Topical medications               | Relevant outcomes include:<br>• Symptoms<br>• Quality of life<br>• Treatment-related morbidity |

## DESCRIPTION

Hyperhidrosis, or excessive sweating, can lead to impairments in psychologic and social functioning. Various treatments for hyperhidrosis are available, such as topical antiperspirant agents (e.g., aluminum chloride 20% solution), oral medications, botulinum toxin, and surgical procedures.

## SUMMARY OF EVIDENCE

### PRIMARY FOCAL HYPERHIDROSIS

#### Iontophoresis

For individuals who have primary focal hyperhidrosis (i.e., axillary, palmar, plantar, craniofacial) who receive iontophoresis, the evidence includes a systematic review, a randomized controlled trial (RCT), and case series. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The RCT found that iontophoresis was less effective than botulinum toxin in the short-term treatment of palmar hyperhidrosis. Additional RCTs are needed comparing iontophoresis with sham or active treatment in patients with various types of primary focal hyperhidrosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### Botulinum Toxins

For individuals who have primary axillary hyperhidrosis who receive botulinum toxin type A or B, the evidence includes RCTs and a meta-analysis. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. Placebo-controlled randomized trials have generally found better outcomes in the botulinum toxin groups. A meta-analysis showed that botulinum toxin injections significantly decreased sweating in the short (two to four weeks) and long term (16 weeks), and significantly improved Hyperhidrosis Disease Severity Scale scores. Several RCTs have compared different botulinum toxin type A formulations with botulinum toxin type A and B formulations in patients with axillary hyperhidrosis. Although these studies had small sample sizes, their findings suggested that, with appropriate dosage adjustments, there are similar levels of efficacy and adverse events. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary palmar hyperhidrosis who receive botulinum toxin type A, the evidence includes RCTs. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. Placebo-controlled randomized trials have generally found better outcomes in the botulinum toxin groups. RCTs comparing botulinum toxin type A formulations in patients with primary palmar hyperhidrosis have generally found no significant differences in outcomes. Although these studies had small sample sizes, their findings suggested that,

with appropriate dosage adjustments, there are similar levels of efficacy and adverse events. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary palmar hyperhidrosis who receive botulinum toxin type B, the evidence includes an RCT. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. One small placebo-controlled randomized trials did not clearly demonstrate the efficacy of botulinum toxin type B in patients with palmar hyperhidrosis. Also, a high rate of adverse events was reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have primary plantar hyperhidrosis who receive botulinum toxin type A or B, the evidence includes no RCTs. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. RCTs are needed comparing botulinum toxin with placebo or active treatment in patients who had primary plantar hyperhidrosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### Microwave

For individuals who have primary focal hyperhidrosis (i.e., axillary, palmar, plantar, craniofacial) who receive microwave treatment, the evidence includes a systematic review, an RCT, and case series. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The RCT, conducted in patients with primary axillary hyperhidrosis, found a short-term benefit of microwave treatment versus sham therapy, but there was a high rate of skin-related adverse events. Additional RCTs are needed comparing radiofrequency ablation with sham or active treatment in patients with various types of primary focal hyperhidrosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### Radiofrequency Ablation

For individuals who have primary focal hyperhidrosis (i.e., axillary, palmar, plantar, craniofacial) who receive radiofrequency ablation, the evidence includes a nonrandomized cohort study. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The cohort study, conducted in patients with palmar hyperhidrosis, found a higher cure rate in the surgery group than in the radiofrequency ablation group and found a similar rate of compensatory sweating in both groups. RCTs are needed comparing radiofrequency ablation with sham or active treatment in patients with various types of primary focal hyperhidrosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### Surgery

For individuals who have primary axillary hyperhidrosis who receive surgical excision of axillary sweat glands, the evidence includes review articles. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The evidence has shown that excision is highly effective, and this treatment is considered standard of care for this indication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary axillary and palmar hyperhidrosis who receive endoscopic transthoracic sympathectomy, the evidence includes several RCTs, a meta-analysis, and case series. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The meta-analysis found a high rate of clinical efficacy after endoscopic transthoracic sympathectomy, although the rate of postoperative compensatory sweating was substantial. Subsequent studies have supported these findings. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary plantar hyperhidrosis who receive lumbar sympathectomy, the evidence includes case series. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. Case series have reported high rates of clinical efficacy, but findings are inconclusive due to lack of control groups. Moreover, there have been substantial rates of compensatory sweating and concerns about adverse events on sexual functioning. The evidence is insufficient to determine the effects of the technology on health outcomes.

## SECONDARY GUSTATORY HYPERHIDROSIS

For individuals who have severe secondary gustatory hyperhidrosis who receive iontophoresis or botulinum toxin, the evidence includes uncontrolled studies and systematic reviews. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The systematic reviews did not identify any relevant RCTs. RCTs are needed to evaluate the safety and efficacy of these treatments for severe secondary gustatory hyperhidrosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have severe secondary gustatory hyperhidrosis who receive tympanic neurectomy, the evidence includes uncontrolled studies and systematic reviews. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. This treatment has high success rates, without the need for repeated interventions, and is considered standard of care for this indication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

## POLICY

Treatment of primary focal hyperhidrosis using the following therapies (see Table 1) may be considered **medically necessary** with any of the following medical conditions:

- acrocyanosis of the hands; or
- history of recurrent skin maceration with bacterial or fungal infections; or
- history of recurrent secondary infections; or
- history of persistent eczematous dermatitis despite medical treatments with topical dermatologic or systemic anticholinergic agents.

Treatment of hyperhidrosis is considered **not medically necessary** in the absence of functional impairment or any of the above medical conditions.

Table PG1 summarizes the treatments that may be considered **medically necessary** by focal region.

Table PG2 summarizes the treatments that are considered **investigational** by focal region.

Table PG1. Treatments for Hyperhidrosis Considered **Medically Necessary**

| Focal Regions | Treatments considered Medically Necessary  |
|---------------|--|
| Axillary      | <ul style="list-style-type: none"> <li>• Aluminum chloride 20% solution</li> <li>• Botulinum toxin* for severe primary axillary hyperhidrosis inadequately managed with topical agents, in patients 18 years of age or older</li> <li>• ETS and surgical excision of axillary sweat glands, if conservative treatment (i.e., aluminum chloride or botulinum toxin*, individually and in combination) has failed</li> </ul> |
| Palmar        | <ul style="list-style-type: none"> <li>• Aluminum chloride 20% solution</li> <li>• Botulinum toxin type A* products for severe primary palmar hyperhidrosis inadequately managed with topical agents, in patients 18 years of age or older</li> <li>• ETS, if conservative treatment (i.e., aluminum chloride or botulinum toxin type A*, individually and in combination) has failed</li> </ul>                           |
| Plantar       | <ul style="list-style-type: none"> <li>• Aluminum chloride 20% solution</li> </ul>   |
| Craniofacial  | <ul style="list-style-type: none"> <li>• Aluminum chloride 20% solution</li> <li>• ETS, if conservative treatment (i.e., aluminum chloride) has failed</li> </ul>  |

Aluminum chloride solution is approved by FDA for treatment of primary hyperhidrosis. At least one botulinum toxin product is FDA-approved for treatment in adults of severe axillary hyperhidrosis inadequately managed by topical agents.

ETS: endoscopic transthoracic sympathectomy; FDA: Food and Drug Administration.

Table PG2. Treatments for Hyperhidrosis Considered **Investigational**

| Focal Regions | Treatments Considered Investigational   |
|---------------|---|
| Axillary      | <ul style="list-style-type: none"> <li>• Axillary liposuction</li> <li>• Iontophoresis</li> <li>• Microwave treatment</li> <li>• Radiofrequency ablation</li> </ul>                             |
| Palmar        | <ul style="list-style-type: none"> <li>• RimabotulinumtoxinB</li> <li>• Iontophoresis</li> <li>• Microwave treatment</li> <li>• Radiofrequency ablation</li> </ul>                              |
| Plantar       | <ul style="list-style-type: none"> <li>• Botulinum toxin*</li> <li>• Iontophoresis</li> <li>• Lumbar sympathectomy</li> <li>• Microwave treatment</li> <li>• Radiofrequency ablation</li> </ul> |
| Craniofacial  | <ul style="list-style-type: none"> <li>• Botulinum toxin*</li> <li>• Iontophoresis</li> <li>• Microwave treatment</li> <li>• Radiofrequency ablation</li> </ul>                                 |

The following treatments may be considered **medically necessary** for the treatment of severe secondary gustatory hyperhidrosis (see Policy Guidelines for list of gustatory hyperhidrosis conditions):

- aluminum chloride 20% solution
- surgical options (i.e., tympanic neurectomy), if conservative treatment has failed.

Other treatments are considered **investigational** as a treatment for severe secondary gustatory hyperhidrosis including, but not limited to iontophoresis.

*\*For guidelines on use of botulinum toxin products refer to the Drug Therapy Guidelines.*

## POLICY GUIDELINES

See also the Cosmetic vs. Reconstructive Services Protocol.

See Drug Therapy Guidelines for botulinum toxin products policy.

A multispecialty working group has defined primary focal hyperhidrosis as a condition that is characterized by visible, excessive sweating of at least six months in duration without apparent cause and with at least two of the following features: bilateral and relatively symmetric sweating, impairment of daily activities, frequency of at least once per week, age at onset younger than 25 years, positive family history, and cessation of focal sweating during sleep.

The Hyperhidrosis Disease Severity Scale is used by patients to rate the severity of their symptoms on a scale of 1 to 4 (see Table PG3).

Table PG3. The Hyperhidrosis Disease Severity Scale

| Score | Definition  |
|-------|---|
| 1     | • My underarm sweating is never noticeable and never interferes with my daily activities      |
| 2     | • My underarm sweating is tolerable but sometimes interferes with my daily activities         |
| 3     | • My underarm sweating is barely tolerable and frequently interferes with my daily activities |
| 4     | • My underarm sweating is intolerable and always interferes with my daily activities          |

Gustatory hyperhidrosis conditions

- Frey syndrome
- encephalitis
- syringomyelia
- diabetic neuropathies
- herpes zoster parotitis
- parotid abscess.

### MEDICARE ADVANTAGE

For Medicare Advantage members the above guidelines will apply, except for the following.

Iontophoresis will be considered **medically necessary** for treatment of intractable, disabling primary focal hyperhidrosis that has not been responsive to recognized standard therapy.

OnabotulinumtoxinA is considered **medically necessary** for treatment of severe primary axillary hyperhidrosis (primary focal hyperhidrosis\*) that is inadequately managed with topical therapy.

### MEDICARE ADVANTAGE POLICY GUIDELINES

Good hygiene measures, extra-strength antiperspirants (for axillary hyperhidrosis), and topical aluminum chloride should initially be tried.

\*The definition of primary focal hyperhidrosis is severe sweating, beyond physiological needs; focal, visible, severe sweating of at least six (6) months duration without apparent cause with at least two (2) of the following characteristics: bilateral and relatively symmetric, significant impairment in daily activities, age of onset less than 25 years, positive family history, and cessation of focal sweating during sleep.

### BACKGROUND

#### HYPERHIDROSIS

Hyperhidrosis has been defined as excessive sweating, beyond a level required to maintain normal body temperature, in response to heat exposure or exercise. It can be classified as primary or secondary. Primary focal hyperhidrosis is idiopathic, typically involving the hands (palmar), feet (plantar), or axillae (underarms). Secondary hyperhidrosis can result from a variety of drugs (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors) or underlying diseases/conditions (e.g., febrile diseases, diabetes; menopause). Secondary hyperhidrosis is usually generalized or craniofacial sweating.

Secondary gustatory hyperhidrosis is excessive sweating on ingesting highly spiced foods. This trigeminovascular reflex typically occurs symmetrically on the scalp or face and predominately over the forehead, lips, and nose. Secondary facial gustatory occurs independently of the nature of the ingested food. This phenomenon frequently occurs after injury or surgery in the region of the parotid gland. Frey syndrome is an uncommon type of secondary gustatory hyperhidrosis that arises from injury to or surgery near the parotid gland resulting in damage to the secretory parasympathetic fibers of the facial nerve. After the injury, these fibers regenerate, and miscommunication occurs between them and the severed postganglionic sympathetic fibers that supply the cutaneous sweat glands and blood vessels. The aberrant connection results in gustatory sweating and facial

flushing with mastication. Aberrant secondary gustatory sweating follows up to 73% of surgical sympathectomies and is particularly common after bilateral procedures.

The consequences of hyperhidrosis are primarily psychosocial. Symptoms such as fever, night sweats, or weight loss require further investigation to rule out secondary causes. Sweat production can be assessed with the Minor starch-iodine test, which is a simple qualitative measure to identify specific sites of involvement.

#### Treatment

A variety of therapies have been investigated for primary hyperhidrosis, including topical therapy with aluminum chloride, oral anticholinergic medications, iontophoresis, intradermal injections of botulinum toxin, endoscopic transthoracic sympathectomy, and surgical excision of axillary sweat glands. Treatment of secondary hyperhidrosis focuses on treatment of the underlying cause, such as discontinuing certain drugs or hormone replacement therapy as a treatment for menopausal symptoms.

Iontophoresis uses electrical current to deliver medication transdermally. A charged ionic drug is placed on the skin with an electrode of the same charge, which drives the drug into the skin, with the purpose of achieving better penetration of the drug into underlying tissue. The benefits of this method would be an enhancement of treatment effects and a reduction in adverse events associated with systemic administration of the drug.

Botulinum toxin is a potent neurotoxin that blocks cholinergic nerve terminals, which prevents hyperstimulation of eccrine sweat glands that lead to excessive sweating. Therefore, intracutaneous injections have been investigated as a treatment of gustatory hyperhidrosis and focal primary hyperhidrosis, most frequently involving the axillae or palms. The drawback of this approach is the need for repeated injections, which have led some to consider surgical approaches.

Surgical treatment options include removal of the eccrine glands and/or interruption of the sympathetic nerves. Eccrine sweat glands produce an aqueous secretion, the overproduction of which is primarily responsible for hyperhidrosis. These glands are innervated by the sympathetic nervous system. Surgical removal has been performed in patients with severe isolated axillary hyperhidrosis.

Various surgical techniques of sympathectomy have been tested. The second (T2) and third (T3) thoracic ganglia are responsible for palmar hyperhidrosis, the fourth (T4) thoracic ganglion controls axillary hyperhidrosis, and the first (T1) thoracic ganglion controls craniofacial hyperhidrosis. Thoracic sympathectomy has been investigated as a potentially curative procedure, primarily for combined palmar and axillary hyperhidrosis unresponsive to nonsurgical treatments. While accepted as an effective treatment, sympathectomy is not without complications. In addition to the immediate surgical complications of pneumothorax or temporary Horner syndrome, compensatory sweating on the trunk generally occurs in most patients, with different degrees of severity. Medical researchers have investigated whether certain approaches (e.g., T3 sympathectomy versus T4 sympathectomy) result in less compensatory sweating, but there remains a lack of consensus about which approach best minimizes the risk of this adverse event. Also, with lumbar sympathectomy for plantar hyperhidrosis, there has been concern about the risk of postoperative sexual dysfunction in both men and women.

#### Outcome Measures

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the Hyperhidrosis Disease Severity Scale has had a good correlation to other assessment tools and is practical in the clinical setting.

#### REGULATORY STATUS

Drysol™ (Person and Covey), an aluminum chloride (hexahydrate) 20% topical solution, was approved by the U.S. Food and Drug Administration (FDA) as an aid in the management of hyperhidrosis (axillae, palmar, plantar,



craniofacial); it is available by prescription. Additional topical medicines approved by the FDA include Hypercare Topical and Xerac AC.

In 2004, botulinum toxin type A (Botox®; Allergan Pharmaceuticals Ireland) was approved by the FDA through the biologic license application process for use to treat primary axillary hyperhidrosis (severe underarm sweating) that cannot be managed by topical agents. In 2009, this product was renamed onabotulinumtoxinA. Other botulinum toxin products approved by FDA for treatment of hyperhidrosis through the biologic license application process include:

2000: RimabotulinumtoxinB (Myobloc®; Solstice Neurosciences)

2009: AbobotulinumtoxinA (Dysport®; Medicis Pharmaceutical)

2010: IncobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals).

None of the other botulinum toxin products is specifically approved for treatment of hyperhidrosis. In 2009, FDA approved the following revisions to the prescribing information of botulinum toxin products:

- “A Boxed Warning highlighting the possibility of experiencing potentially life-threatening distant spread of toxin effect from injection site after local injection.
- A Risk Evaluation and Mitigation Strategy (REMS) that includes a Medication Guide to help patients understand the risk and benefits of botulinum toxin products.
- Changes to the established drug names to reinforce individual potencies and prevent medication errors. The potency units are specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from one product to another botulinum toxin product. The new established names reinforce these differences and the lack of interchangeability among products.”

In 2011, the miraDry® System (Miramar Labs) was cleared for marketing by FDA through the 510(k) process for treating primary axillary hyperhidrosis. This microwave device is designed to heat tissue at the dermal-hypodermal interface, the location of the sweat glands. Treatment consists of two sessions for a total duration of approximately one hour. Sessions occur in a physician’s office, and a local anesthetic is used. The device is currently not approved for the treatment of palmar or plantar hyperhidrosis.

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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46. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Determination (LCD): Botulinum Toxins (L33646), Revision Effective Date for services performed on or after 06/16/2017.