Select Health Medical Policies

Pharmacology Policies

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Select Health

MEDICAL POLICY

COMPOUNDED MEDICATIONS

Policy # 674

Implementation Date: 12/21/06

Review Dates: 2/18/10, 2/17/11, 2/16/12, 4/25/13, 2/20/14, 3/19/15, 2/11/16, 2/16/17, 2/15/18, 1/31/19, 2/4/20, 2/1/21, 1/11/22, 2/16/23, 1/30/24, 2/13/25

Revision Dates: 2/21/08, 2/19/09

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

The FDA defines drug compounding as the process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to an individual patient's needs. Government legislation, such as the Federal Drug and Cosmetic Act (FDCA) of 1938, and the Food and Drug Administration Modernization Act (FDAMA) of 1997, exempts drug compounding, so long as providers of the compounded drugs abide by several restrictions listed in the FDA Compliance. To be covered, a compounded prescription must contain at least one federal legend drug in therapeutic amounts. A federal legend drug is defined as a medication product that by Federal law bears the statement "Caution – Federal (U.S.A.) law prohibits dispensing without a prescription" or words of similar meaning (such as "Rx only").

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

For plans with RxSelect formularies, Select Health covers compounded medications *in limited circumstances,* as described below, consistent with current FDA guidelines. Coverage in these circumstances is believed to be medically necessary. Any compounded medication used which does not meet these requirements is considered experimental/investigational and may not be covered.

A compounded prescription is considered medically necessary when ALL the following criteria are met:

1. The active ingredient in the compounded product contains at least one legend medication component.
2. The legend medication is FDA approved for medical use in the United States.
3. The active medication component is in therapeutic amounts, based on scientific literature or national compendia.
4. The safety and effectiveness for the compounded medication and its route of administration (including the delivery system) is supported by scientific literature or national compendia.

If a compound is similar to a commercially available product, but differs from the commercially available product in dosage, dosage form, and/or omission of dye, sweetener, flavoring, or preservative, then clinical documentation is required from the prescriber supporting the clinical need for the compound.

Select Health does NOT cover compounded "bio-identical" hormone replacement therapy (BHRT). Prescriptions for BHRT can be uniquely formulated; therefore, coverage will be based on the drug NDC code being submitted for reimbursement. Benefits will be determined based on our standard coverage for compounded medications. All pharmacy benefit limitations and exclusions apply.

Select Health

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Drug compounding is defined as the process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to an individual patient's needs. The FDA recognizes pharmacists or physicians to engage in traditional extemporaneous drug compounding of reasonable quantities of drugs on response and receipt of a valid prescription. Drug compounding may be required to fit the medical needs of a patient because a medication is not commercially available in the strength or dosage form. Drug compounding may also be required for:

- Preparation of a medication that has been withdrawn from the market for economic concerns, NOT safety
- Patients that cannot or may have trouble swallowing and require liquid formulations or rectal suppositories
- Patients that may have allergies to dyes, preservatives, or fillers in commercial products and require allergy-free medications

Drug compounding for the purposes of convenience is not considered medically necessary. The FDA provides rules and guidance to assure compounding activities performed by pharmacies and/or physician offices are maintained within the realm of traditional pharmacy practice and that activities are not those that would be considered manufacturing and distributing of an unapproved new drug. Regulation of compounding is generally done at the state level. States may vary in their regulation and definitions of compounding.

"Bio-identical" hormone therapy (BHRT) is commonly prescribed as compounded medications. The term "bio-identical" has no defined meaning in any medical or conventional dictionary, and the FDA does not recognize the term. Even different medical groups define the term differently. Select Health defines bio-identical hormone therapy as the supplementation of hormones that are biochemically similar or identical to those produced by the body.

The safety and efficacy of compounded BHRT has not been documented in clinical studies. Additionally, there is no sound evidence showing that the side effects and risks of compounded BHRT drugs are different than those of similarly formulated FDA-approved menopausal hormone therapy drugs and they are expected to have the same benefits and risks associated with FDA-approved hormone therapy.

Billing/Coding Information

CPT CODES

No specific codes identified

HCPCS CODES

J7999 Compounded drug, not otherwise classified

Select Health

Compounded Medications, continued

Key References
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2. Federal Food and Drug Administration. The practice of pharmacy compounding. www.fda.gov/cder/pharmcomp/default.htm. Accessed February 11, 2008.

Disclaimer

This document is for informational purposes only and should not be relied on in the diagnosis and care of individual patients. Medical and Coding/Reimbursement policies do not constitute medical advice, plan preauthorization, certification, an explanation of benefits, or a contract. Members should consult with appropriate healthcare providers to obtain needed medical advice, care, and treatment. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the member's individual benefit plan that is in effect at the time services are rendered.

The codes for treatments and procedures applicable to this policy are included for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Select Health® makes no representations and accepts no liability with respect to the content of any external information cited or relied upon in this policy. Select Health updates its Coverage Policies regularly, and reserves the right to amend these policies without notice to healthcare providers or Select Health members.

Members may contact Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Coverage Policy may call Select Health Provider Relations at (801) 442-3692.

Select Health

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MEDICAL POLICY

DIAGNOSTIC TESTING FOR CHRONIC FATIGUE SYNDROME (CFS)

Policy # 288
Implementation Date:12/10/05
Review Dates: 12/21/06, 12/20/07, 12/18/08, 12/17/09, 2/16/12, 4/25/13, 2/20/14, 3/19/15, 2/11/16, 2/16/17, 2/15/18, 2/27/19, 2/17/20, 2/18/21,1/25/22, 2/5/23, 2/4/24, 1/31/25
Revision Dates: 2/17/11, 2/4/22, 2/21/23

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description
The 2015 IOM diagnostic criteria for myalgic encephalomyletis/chronic fatigue syndrome (ME/CFS) in adults and children state that three symptoms and at least one of two additional manifestations are required for diagnosis. The three required symptoms are:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of activity (occupational, educational, social, or personal life) that:

    a) lasts for more than 6 months

    b) is accompanied by fatigue that is:

        i. often profound

        ii. of new onset (not life-long)

        iii. not the result of ongoing or unusual excessive exertion

        iv. not substantially alleviated by rest

2. Post-exertional malaise (PEM)*—worsening of symptoms after physical, mental, or emotional exertion that would not have caused a problem before the illness. PEM often puts the patient in relapse that may last days, weeks, or even longer. For some patients, sensory overload (light and sound) can induce PEM. The symptoms typically get worse 12 to 48 hours after the activity or exposure and can last for days or even weeks.

3. Unrefreshing sleep* - patients with ME/CFS may not feel better or less tired even after a full night of sleep despite the absence of specific objective sleep alterations.

<u>At least one of the following two additional manifestations must be present:</u>

1. Cognitive impairment* - patients have problems with thinking, memory, executive function, and information processing, as well as attention deficit and impaired psychomotor functions. All can be exacerbated by exertion, effort, prolonged upright posture, stress, or time pressure, and may have serious consequences on a patient's ability to maintain a job or attend school full time.

2. Orthostatic intolerance - patients develop a worsening of symptoms upon assuming and maintaining upright posture as measured by objective heart rate and blood pressure abnormalities during standing, bedside orthostatic vital signs, or head-up tilt testing. Orthostatic symptoms including lightheadedness, fainting, increased fatigue, cognitive worsening, headaches, or nausea are worsened with quiet upright posture (either standing or sitting) during day-to-day life and are improved (though not necessarily fully resolved) with lying down. Orthostatic intolerance is often the most bothersome manifestation of ME/CFS among adolescents.

*The frequency and severity of these symptoms need to be evaluated. The IOM committee specified that "The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity."

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers exclusionary diagnostic tests for chronic fatigue syndrome (CFS) in *limited circumstances* as supported by the NIH consensus panel.

Covered diagnostic tests for CFS:

- Antinuclear antibodies (ANA)
- Blood and serum chemistries (serum electrolytes, blood urea nitrogen [BUN], glucose, calcium, magnesium, creatinine)
- Complete blood count (CBC) with differential white blood count
- C-reactive protein
- Erythrocyte sedimentation rate (ESR)
- Estradiol/testosterone
- FSH levels
- HIV Serology
- Immunoglobulin levels (in patients with documented recurrent bacterial infections)
- Iron levels
- Liver function tests (LFTs)
- Lyme serology
- MRI of the head (to rule out multiple sclerosis [MS])
- Polysomnography (to rule out sleep apnea)
- Rheumatoid factor (RF)
- Serum cortisol
- Serum protein electrophoresis
- Thyroid function tests – TSH, free T4, T3
- Tuberculosis skin test
- Urinalysis (UA)
- Urine drug screen
- Vitamin B12

Select Health does NOT cover all other diagnostic tests, including, but not limited to the tests outlined below, as they are considered investigational in the evaluation of CFS.

Denied diagnostic tests when used for CFS:

- ELISA/ACT testing
- Evaluation of enteric dysbiosis
- Evaluation of mitochondrial disorders
- Functional elevation of NK cells
- Gene expression profiling
- Measurements of delayed hypersensitivity
- MRI scans (except when there is clinical suspicion for MS)

- Production and response to cytokines
- Quantification of B and T cell subsets
- Quantification of natural killer (NK) cells
- Radionuclide scans such as SPECT and PET
- RNAse L enzymatic activity assay or RNase L protein quantification
- Serologic tests for candida albicans
- T cell response to mitogenic stimulation
- Viral serologies, including, but not limited to:
  - Coxsackie virus serology
  - Enterovirus serology
  - Herpes virus serologies (i.e., Epstein Barr virus, cytomegalovirus [CMV], human herpes virus-6)
  - Retrovirus serologies (except HIV)

SELECT HEALTH MEDICARE (CMS)

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Summary of Medical Information

In the revised definition, a consensus viewpoint from many of the leading CFS researchers and clinicians (including input from patient group representatives), chronic fatigue syndrome is treated as a subset of chronic fatigue, a broader category defined as unexplained fatigue of greater than or equal to 6 month's duration. Chronic fatigue, in turn, is treated as a subset of prolonged fatigue, which is defined as fatigue lasting 1 or more months. The expectation is that scientists will devise epidemiologic studies of populations with prolonged fatigue and chronic fatigue, and search within those populations for illness patterns consistent with CFS.

In addition to a thorough history and physical examination, recommended procedures for evaluating patients suspected of having chronic fatigue syndrome include a mental status examination to identify abnormalities in mood, intellectual function, memory, and personality. Evidence of psychiatric, neurologic, or cognitive disorder requires that an appropriate psychiatric, psychological, or neurological evaluation be done.

Laboratory tests include a complete blood count with differential cell count, an erythrocyte sedimentation rate, a chemistry profile including liver function tests, thyroid function test (either a thyroid panel or thyroid stimulating hormone), antinuclear antibodies, and urinalysis. Additional tests, if indicated, include rheumatoid factor, immunoglobulin levels, tuberculin skin test, Lyme disease serology (if patient lives in an endemic area), HIV serology, MRI of the head (if indicated to rule out multiple sclerosis), and polysomnography (if indicated to rule out a sleep disorder).

The following tests do not confirm or exclude the diagnosis of chronic fatigue syndrome: serologic tests for Epstein-Barr virus, retroviruses (except HIV), human herpes virus-6, enteroviruses, and Candida albicans; and tests of immunologic function, including cell population and function studies.

Immunologic abnormalities in patients with suspected (CFS) is an active area of research into the pathogenesis of CFS. However, the published literature is inadequate to determine the sensitivity, specificity, and positive and negative predictive values of these tests. Most of the research has compared the immunologic function of patients with CFS with healthy normal controls, so that it is impossible to know whether the subtle immunologic abnormalities seen are specific to CFS or are also present in patients with conditions that have similar symptoms.

Although it was originally thought that CFS was related to a viral etiology, more recent studies have failed to find any predictable association between CFS and any particular virus.

An NIH consensus conference recommended a list of exclusionary laboratory tests that were considered appropriate for the work-up of a patient with suspected CFS. Since that time, there have been investigations into the immune function of patients with CFS, such as quantitative studies of natural killer cells, B and T cell subsets, and the production of cytokines, such as interferons and interleukin-2. Assessments of these immunologic parameters have produced conflicting results, in part related to varying methodologies used, the heterogeneity of patients who are tested at different points in their disease, and the dynamic nature of the immune system which makes assessment of single tests difficult. While assessments of levels of IgG subsets have shown a decrease in IgG1 and IgG3, the studies were performed on small numbers of patients with undefined control groups or only healthy controls. Therefore, it is not unexpected that the published data fail to indicate the sensitivity, specificity, positive and negative predictive value of the above immunologic tests. While immune function may provide a fertile path for research, its use in the clinical diagnosis and management of CFS is still investigational.

McCully et al. examined the association between CFS-reduced blood flow and muscle oxidative metabolism. Muscle blood flow was measured in the femoral artery with Doppler ultrasound after exercise. Muscle metabolism was measured in the medial gastrocnemius muscle with P-magnetic resonance spectroscopy. Muscle oxygen saturation and blood volume were measured using near-infrared spectroscopy. The authors concluded that CFS patients showed evidence of reduced hyperemic flow and reduced oxygen delivery, but no evidence either resulted in impaired muscle metabolism. Thus, CFS patients might have altered control of blood flow, but this is unlikely to influence muscle metabolism. In addition, abnormalities in muscle metabolism do not appear to be responsible for the CFS symptoms.

Billing/Coding Information
Covered: For the conditions outlined above

CPT CODES

70551	Magnetic resonance (e.g., proton) imaging, brain (including brain stem); without contrast material
70552	Magnetic resonance (e.g., proton) imaging, brain (including brain stem); with contrast material(s)
70553	Magnetic resonance (e.g., proton) imaging, brain (including brain stem); without contrast material, followed by contrast material(s) and further sequences
80048	Basic metabolic panel (calcium, total)
80050	General health panel
80051	Electrolytes panel
81000	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, ph, protein, spec gravity, urobilinogen, any number of these constituents; non-automated, with microscopy
81001	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, ph, protein, spec gravity, urobilinogen, any number of these constituents; automated with microscopy

Diagnostic Testing for Chronic Fatigue Syndrome (CFS), continued

81002	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, ph, protein, spec gravity, urobilinogen, any number of these constituents; non-automated, without microscopy
81003	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, ph, protein, spec gravity, urobilinogen, any number of these constituents; automated, without microscopy
81015	Urinalysis; microscopic only
81020	Urinalysis; two or three glass test
81050	Volume measurement for timed collection, each
82784	Gammaglobulin; IGA, IGD, IGG, IGM, each
82785	Gammaglobulin; IGE
82787	Gammaglobulin; immunoglobulin subclasses, (IGG1, 2, 3, OR 4), each
82530	Cortisol; free
82533	Cortisol; total
83001	Gonadotropin; follicle stimulating hormone (FSH)
83735	Magnesium
84165	Protein; electrophoretic fractionation and quantitation, serum
84439	Thyroxine; free
84443	Thyroid stimulating hormone (TSH)
84479	Thyroid hormone (T3 or T4) uptake or thyroid hormone binding ratio (THBR)
84481	Triiodothyronine (T-3); free
85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count
85651	Sedimentation rate, erythrocyte, non-automated
85652	Sedimentation rate, erythrocyte; automated
86038	Antinuclear antibodies (ANA)
86430	Rheumatoid factor; qualitative
86431	Rheumatoid factor; quantitative
86580	Skin test; tuberculosis, intradermal
86617	Antibody; borrelia burgdorferi (lyme disease) confirmatory test (e.g., western blot or immunoblot)
86618	Antibody; borrelia burgdorferi (Lyme disease)
86689	Antibody; HTLV or HIV antibody, confirmatory test (e.g., western blot)
86701	Antibody; HIV -1
86702	Antibody; HIV -2
86703	Antibody; HIV -1 and HIV -2, single assay
95808	Polysomnography; sleep staging with 1-3 additional parameters of sleep, attended by a technologist
95810	Polysomnography; sleep staging with 4 or more additional parameters of sleep, attended by a technologist

95811 Polysomnography; sleep staging with 4 or more additional parameters of sleep, with initiation of continuous positive airway pressure therapy or bilevel ventilation, attend by a technologist

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Revision History

Revision Date	Summary of Changes
2/21/23	For Commercial Plan Policy, added four diagnostic tests to list of exclusions: "- RNAse L enzymatic activity assay or RNase L protein quantification - Gene expression profiling - Evaluation of mitochondrial disorders - Evaluation of enteric dysbiosis"

Select Health

MEDICAL POLICY

ESTRADIOL PELLETS FOR ESTROGEN REPLACEMENT

Policy # 256
Implementation Date: 12/30/04
Review Dates: 12/15/05, 12/21/06, 12/20/07, 12/18/08, 12/19/09, 10/21/10, 12/15/11, 7/18/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 7/20/18, 6/17/19, 6/1/20, 6/1/21, 5/11/22, 6/15/23, 5/31/24
Revision Dates:

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Description
Estradiol pellets consist of a pharmacy-compounded substance where each pellet consists of a hard crystal of 17 beta estradiol (the natural estrogen produced by the human ovary) which releases into the blood stream, attains a steady state, and then will get used up as the estrogen is metabolized in the body. These implants are proposed to provide a very steady estrogen level of approximately 150–250 picograms/ml, which is a therapeutic level. Each pellet lasts from 3 to 4 months.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover the implantation of estradiol pellets for the treatment of menopausal symptoms or other hormonal deficiencies. This therapy meets the plan's definition of experimental/investigational.

SELECT HEALTH ADVANTAGE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Summary of Medical Information
Implantable estradiol pellets have been suggested as treatment for symptoms of menopause. There are no FDA approved, commercially available formulations of implantable estradiol pellets available in the United States. These formulations of estradiol have been shown to produce unpredictable and fluctuating serum concentrations of estrogen. The U.S. Food and Drug Administration's (FDA) Fertility and Maternal Health Drugs Advisory Committee unanimously agreed to terminate compassionate investigative new

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drug (IND) programs for estrogen pellets as a last-resort treatment of menopausal disorder. The committee noted: "… the risk of bleeding and infection, the lack of information on release rates, difficulty in reversibility of the drug, increased feasibility of over dosage of the drug, and increased risk of non-compliance with safety measures [such as] the addition of progestin."

Billing/Coding Information

CPT CODES

11980	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)
11982	Removal, non-biodegradable drug delivery implant
11983	Removal with reinsertion, non-biodegradable drug delivery implant

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MEDICAL POLICY

IV ANTIBIOTIC THERAPY FOR LYME DISEASE

Policy # 576
Implementation Date:2/22/16
Review Dates: 2/16/17, 6/21/17, 7/20/18, 6/16/19, 6/4/20, 6/11/21, 5/18/22, 6/15/23, 5/31/24
Revision Dates:

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Lyme disease is a multisystem inflammatory disease caused by Borrelia burgdorferi and transmitted by the bite of an infected ixodid tick. Oral antibiotics usually are adequate for treatment of Lyme disease, but in some cases, a 2−4-week course of intravenous (IV) antibiotics may be appropriate such as in cases of Lyme arthritis, carditis, or objective neurologic complications. Evidence has not shown a benefit to prolonged (greater than 4 weeks) or repeat courses of IV antibiotics. Therefore, repeat or prolonged courses of antibiotic therapy are considered not medically necessary.

The evidence for polymerase chain reaction–based detection of B burgdorferi in individuals who are suspected of having Lyme disease includes a review of the evidence with recommendations from the Centers for Disease Control and Prevention on tiered diagnostic testing. Relevant outcomes are test accuracy and validity, change in disease status, and morbid events. The optimum method of testing depends on the stage of the disease. Diagnostic testing may not be necessary when a diagnosis can be made clinically in patients with a recent tick bite or exposure and the presence of the characteristic rash of erythema migrans. When laboratory studies are needed, serologic testing using the 2-step ELISA followed by Western blot is the recommended first approach. Polymerase chain reaction (PCR), may be considered medically necessary as a second approach in patients with a short duration of neurologic symptoms (< 14 days) or uncertainty in serologic testing. The evidence is considered sufficient to determine qualitatively that the technology results in an improvement in the net health outcome. For detection of B. burgdorferi, only the amplified probe technique is used clinically. The direct probe technique is not clinically useful due to the small numbers of organisms present. The quantification technique has no clinical role at this time since treatment decisions are not based on the quantification of organisms present. Other uses for PCR-based testing are considered investigational.

The evidence for other diagnostic tests in individuals who are suspected of having Lyme disease is limited. Relevant outcomes are test accuracy, change in disease status, and morbid events. Evidence for PCR-based testing in situations other than the approach described above is limited. There is little clinical utility in genotyping or phenotyping of B burgdorferi. Additional research is necessary to determine diagnostic and treatment utility of the CXCL13, and its use is considered investigational. Other diagnostic testing approaches, such as C6 peptide ELISA, also warrant additional research. Evidence is insufficient to evaluate the effects of the technology on health outcomes.

The evidence for prolonged or repeated courses of antibiotic therapy in individuals with confirmed Lyme disease includes a number of randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, morbid events, and health status measures. Oral antibiotics usually are adequate for treatment of Lyme disease, but, in some cases, a 2- to 4-week course of intravenous (IV) antibiotics may be appropriate in cases of Lyme arthritis, carditis, or objective neurologic complications. Evidence from RCTs has not shown a benefit to prolonged (> 4 weeks) or repeat courses of oral or IV antibiotics. The evidence is sufficient to determine quantitatively that the technology is unlikely to improve the net health outcome.

COMMERCIAL PLAN POLICY/CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers IV antibiotics in the treatment of Lyme disease *in limited circumstances* when oral antibiotics have failed to eradicate the infection, or the patient is unable to take oral antibiotics.

Coverage Criteria:

A course of up to 4 weeks of intravenous (IV) antibiotic therapy is considered **medically necessary** for individuals with laboratory-confirmed Lyme disease whose diagnosis has been established by a board-certified infectious disease specialist, meeting **ANY** of the following criteria:

1. Myocarditis associated with second- or third-degree atrioventricular block, or with first-degree heart block when the PR interval is prolonged to 30 milliseconds or greater; or
2. Persistent or recurrent joint swelling (that is, arthritis) after an initial 1-month trial of oral antibiotics.
3. Acute or chronic neurological disease affecting the central or peripheral nervous system, including **ANY** of the following:
    a. Meningitis
    b. Any neurologic syndrome with cerebrospinal fluid (CSF) pleocytosis
    c. Peripheral neurologic syndromes with normal CSF (including radiculopathy, diffuse neuropathy, mononeuropathy multiplex, or cranial neuropathy), if severe or following treatment failure with oral antibiotic therapy
    d. Encephalomyelitis
    e. Encephalopathy

And antibiotic used is:

- Ceftriaxone (Rocephin), cefotaxime (Claforan), or Penicillin G
- Azithromycin (Zithromax) in individuals with betalactam allergy or intolerance

Select Health does not cover intravenous (IV) antibiotic therapy for individuals with Lyme disease when the above criteria are not met, including when the following IV drugs are used (their use is considered investigational and not medically necessary)**:**

- Carbapenems (for example, doripenem, ertapenem, imipenem, meropenem)
- First-generation cephalosporins (e.g., cefazolin)
- Fluconazole
- Fluoroquinolones (for example, levofloxacin, moxifloxacin).

Select Health does not cover other uses of intravenous (IV) antibiotic therapy for Lyme disease as they are considered investigational and not medically necessary, including, but not limited to any of the following:

1. Prophylactic treatment of individuals who have reported a tick bite but have no clinical findings suggestive of Lyme disease
2. Treatment of chronic fatigue syndrome or fibromyalgia attributed to Lyme disease
3. Initial treatment of Lyme arthritis without coexisting neurological symptoms
4. Treatment of persistent Lyme-associated arthritis after 2 prior courses of antibiotic therapy
5. Repeat or prolonged courses (greater than 4 weeks) of intravenous antibiotics
6. Patients with symptoms consistent with systemic exertion intolerance disease fibromyalgia, in the absence of objective clinical or laboratory evidence for Lyme disease
7. Patients with seronegative Lyme disease in the absence of CSF antibodies
8. Cranial nerve palsy (e.g., Bell's palsy) without clinical evidence of meningitis

9. Antibiotic-refractory Lyme arthritis (unresponsive to 2 courses of oral antibiotics or to 1 course of oral and 1 course of intravenous antibiotic therapy)
10. Patients with vague systemic symptoms without supporting serologic or CSF studies
11. Patients with a positive ELISA test, unconfirmed by an immunoblot or Western blot test
12. Patients with an isolated positive serologic test in the setting of multiple negative serologic studies
13. Patients with chronic (> 6 months) subjective symptoms ("post-Lyme syndrome") after receiving recommended treatment regimens for documented Lyme disease.
    Repeat or prolonged courses (e.g., greater than 4 weeks) of IV antibiotic therapy are considered not medically necessary

Select Health does NOT cover repeat PCR-based direct detection of B. burgdorferi as a justification for continuation of IV antibiotics beyond 1 month in patients with persistent symptoms, or as a technique to follow therapeutic response. Use in these circumstances is considered experimental/investigational.

Select Health does NOT cover certain other testing used to identify Lyme disease for the purpose of treating or following patients who have undergone treatment of Lyme disease as use of this testing is considered experimental/investigational. Excluded tests include the following:

- PCR-based direct detection of B. burgdorferi in urine samples in all clinical situations.
- Genotyping or phenotyping of B. burgdorferi.
- Other diagnostic testing, including, but not limited to C6 peptide ELISA or determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment.
- The direct probe technique and the quantification technique for detection of B. burgdorferi.

Select Health does not cover intramuscular antibiotics as a treatment of any aspect of Lyme disease. Use of intramuscular antibiotics is considered experimental/investigational and not medically necessary**.**

Select Health does not cover any home healthcare services such as nursing visits to administer noncovered antibiotics, maintenance of central venous catheters, or home care supplies for patients in which the IV therapy is not covered.

SELECT HEALTH ADVANTAGE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Short-Term Antibiotic Treatment. Several clinical practice guidelines recommend the use of short-term parental antibiotic treatment (≤ 4 weeks) in patients with Lyme disease (See Professional Societies information below). These recommendations are based on a high-quality body of evidence, derived from

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a number of randomized controlled trials (RCTs), which demonstrate the safety and efficacy for this indication.

Long-Term Antibiotic Treatment. Four randomized, placebo-controlled, double-blinded clinical trials, published as three studies, evaluated antibiotic therapy in patients with chronic Lyme disease. All RCTs were sponsored by the National Institutes of Health (NIH). Patients were either untreated or had failed primary antibiotic treatment. Study size was generally small and ranged from 37 to 78 patients. Patients were administered intravenous (IV) ceftriaxone for a treatment duration that ranged from 28 days to 3 months. One study also administered oral doxycycline for 60 days following 30 days of IV ceftriaxone. Outcome measures were varied, and include biological markers of infection, functional status and/or Health-Related Quality of Life (HR-QOL) measures, cognitive function, mood and psychological measures, fatigue, and pain. These studies, including outcomes, measures, and treatment results are described in detail below.

Fallon et al. (2008) studied patients with mild-to-moderate cognitive impairment and marked levels of fatigue, pain, and impaired physical functioning. Patients had well-documented Lyme disease, with at least 3 weeks of prior intravenous (IV) antibiotics, current positive IgG Western blot, and objective memory impairment. Healthy individuals served as controls for practice effects. Thirty-seven patients were randomly assigned to 10 weeks of double-masked treatment with IV ceftriaxone, or IV placebo, and then no antibiotic therapy. Across six cognitive domains, a significant treatment-by-time interaction favored the antibiotic-treated group at week 12. The improvement was generalized (not specific to domain) and moderate in magnitude, but it was not sustained to week 24. On secondary outcomes, patients with more severe fatigue, pain, and impaired physical functioning who received antibiotics were improved at week 12, and this was sustained to week 24 for pain and physical functioning. IV ceftriaxone therapy resulted in short-term cognitive improvement for patients with post-treatment Lyme encephalopathy, but relapse in cognition occurred after the antibiotic was discontinued.

Krupp et al. (2003) conducted a single-center randomized double-masked placebo-controlled trial on 55 patients with Lyme disease with persistent severe fatigue at least 6 or more months after antibiotic therapy. Patients were randomly assigned to receive 28 days of IV ceftriaxone or placebo. The primary clinical outcomes were improvement in fatigue and cognitive function. The primary laboratory outcome was measure of infection. Outcome data were collected at the 6-month visit. Ceftriaxone therapy in patients with post-Lyme syndrome (PLS) with severe fatigue was associated with an improvement in fatigue but not with cognitive function or laboratory measure of infection. Because fatigue (a nonspecific symptom) was the only outcome that improved and because treatment was associated with adverse events, this study does not support the use of additional antibiotic therapy with parenteral ceftriaxone in post-treatment, persistently-fatigued patients with PLS.

Klempner et al. (2001) conducted two RCTs of extended antibiotic treatment for the same set of patients in whom symptoms persisted after the recommended treatment (n=129) and evaluated quality of life (QOL) outcomes. Seventy-eight patients who were seropositive for IgG antibodies and 51 patients who were seronegative were randomized to receive either intravenous ceftriaxone daily for 30 days, followed by oral doxycycline daily for 60 days or matching intravenous and oral placebos. After completion of treatment with antibiotics, 37 percent of the seropositive group showed improvement in the physical- and mental- component summary scales of the Short-Form General Health Survey, 29 percent had no change, and 34 percent had a worsening of symptoms. In the seropositive patients who received placebo, 40 percent improved, 26 percent had no change, and 34 percent worsened. The results were similar for the seronegative patients in both treatment groups.

Subsequently, Kaplan et al. (2003) evaluated the same 129 patients enrolled in the Klempner et al. (2001) study, and reported neurocognitive outcomes following additional antibiotic therapy. Symptom severity was measured using the cognitive functioning, pain and role functioning scales of the Medical Outcomes Study (MOS). Memory, attention, and executive functioning were assessed using objective tests. Mood was assessed using the Beck Depression Inventory (BDI) and Minnesota Multiphasic Personality Inventory (MMPI). There were no significant baseline differences between seropositive and seronegative groups. Both groups reported a high frequency of MOS symptoms, depression, and somatic complaints but had normal baseline neuropsychological test scores. The combined groups showed significant decreases in MOS symptoms, higher objective test scores, and improved mood between baseline and 90 days. However, there were no significant differences between those receiving antibiotics and placebo. Patients with PTCLD who had symptoms but showed no evidence of persisting Borrelia

infection, did not show objective evidence of cognitive impairment. Additional antibiotic therapy was not more beneficial than administering placebo.

Safety. High rates of adverse events following long-term antibiotic therapy have been observed in the available studies. One study reported that diarrhea occurred more often following antibiotic therapy than placebo treatment (43% versus 25%), and another study reported that rash, diarrhea, and vaginal pruritus occurred more frequently after antibiotic treatment than placebo (14% versus 3%). More serious, life-threatening complications were also reported in some individuals, including anaphylaxis in one patient (Krupp et al., 2003), life-threatening pulmonary embolism in one patient, and anemia accompanied by fever and gastrointestinal bleeding in one patient (Klempner et al., 2001; Hayes, 2010b; updated 2014).

In summary, results of the available RCTs not only failed to demonstrate a prolonged therapeutic effect of long-term antibiotic therapy for chronic Lyme disease, but they also demonstrated a serious risk of harm. The overall body of evidence was of moderate quality, with individual study quality varying from fair to good. However, the evidence is hampered by the small number of available studies, variation in outcome measures across studies, and high dropout rates in some studies. There was some evidence that long-term antibiotic therapy might improve fatigue and conflicting evidence that the treatment might improve neurocognitive measures. However, there was no evidence of the efficacy of antibiotic treatment to improve patient-relevant outcomes, such as functional status and/or quality of life, pain, mood, and psychological measures. Furthermore, there was a high rate of treatment-related adverse events associated with long-term antibiotic therapy, some of which were considered serious and life-threatening. Definitive patient selection criteria for long-term antibiotic therapy for chronic LD have not been established (Hayes, 2010b; updated 2014).

In addition, several professional societies have made statements regarding the use of IV antibiotics for Lyme disease. In 2007 and subsequently reaffirmed in 2014, the American Academy of Neurology (AAN) Quality Standards Subcommittee (QSS) published evidenced-based practice parameters for the treatment of nervous system Lyme disease (Halperin et al., 2007). Their recommendations include:

- Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for CNS Lyme disease with or without parenchymal involvement.
- Recommended duration of both oral and parenteral regimens is 14 days, although the duration of antibiotic therapy in published studies ranged from 10 to 28 days without significantly different outcomes.
- Prolonged courses of antibiotics do not provide beneficial effects in post-Lyme syndrome (PLDS), and antibiotics are potentially associated with adverse events.

The European Federation of Neurological Societies (EFNS) guideline on the diagnosis and management of Lyme disease makes the following recommendations (Mygland et al., 2010):

- Adult patients with definite or possible acute Lyme disease (symptom duration < 6 months) should be offered a single 14-day course of antibiotic treatment. Oral doxycycline (200 mg daily) and intravenous (IV) ceftriaxone (2 g daily) are equally effective in patients with symptoms confined to the peripheral nervous system, including meningitis.
- Patients with central nervous system manifestations should be treated with IV ceftriaxone (2 g daily) for 14 days and late Lyme disease (symptom duration > 6 months) for 3 weeks.
- If symptoms persist for more than 6 months after standard treatment, the condition is often termed post-Lyme disease syndrome (PLDS). Antibiotic therapy has no impact on PLDS.

The Infectious Diseases Society of America (IDSA) guidelines for the treatment of Lyme disease make the following recommendations (Wormser et al., 2006; deemed current 2011):

- In the absence of neurologic or cardiac manifestations, oral antibiotics (e.g. doxycycline, amoxicillin or cefuroxime axetil) are recommended for 14 to 21 days. Intravenous (IV) antibiotics, while effective, are not superior to oral agents and are more likely than the recommended orally administered antimicrobials to cause serious adverse effects. Therefore, IV antibiotics are not recommended for treatment of patients with early Lyme disease and no indication of neurologic or cardiac involvement.

- For patients with early Lyme disease and acute neurologic manifestations of meningitis or radiculopathy, the use of ceftriaxone for 14 to 28 days is recommended. Parenteral therapy with cefotaxime or penicillin G may be a satisfactory alternative.
- Patients with atrioventricular heart block and/or myopericarditis associated with early Lyme disease may be treated with either oral or parenteral antibiotic therapy for 14 to 21 days.
- Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally. However, it is important to recognize that a small number of patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require intravenous therapy with a beta-lactam antibiotic for successful resolution.
- Patients with arthritis plus objective evidence of neurologic disease should receive parenteral therapy with ceftriaxone for 14 to 28 days. Cefotaxime or penicillin G administered parenterally is an acceptable alternative.
- Patients who have persistent or recurrent joint swelling after a recommended course of oral antibiotic therapy should be retreated with another 4-week course of oral antibiotics OR with a 2 to 4-week course of intravenous ceftriaxone. A second 4-week course of oral antibiotic therapy is favored by panel members for the patient whose arthritis has substantively improved but has not yet completely resolved, reserving intravenous antibiotic therapy for those patients whose arthritis failed to improve at all or worsened. Clinicians should consider waiting several months before initiating retreatment with antimicrobial agents because of the anticipated slow resolution of inflammation after treatment.
- Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone for 14 to 28 days. Cefotaxime or penicillin G administered intravenously is an alternative. Response to treatment is usually slow and may be incomplete. Retreatment is not recommended unless relapse is shown by reliable objective measures.
- Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (≥ 6 months) subjective symptoms after administration of recommended treatment regimens for Lyme disease.
- Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data or the potential for harm to the patient, long-term (> 28 days) antibiotic therapy is not recommended for treatment of patients with any manifestation of Lyme disease.
- Multiple, repeated courses of antimicrobials for the same episode of Lyme disease is not recommended.

In 2008, a review panel was convened to determine whether the IDSA's guidelines were based on sound scientific evidence and whether revisions were needed. Based on its review of all the evidence, the review panel determined that no changes or revisions to the 2006 IDSA guidelines were necessary. The panel's conclusions, which are consistent with those reached by the IDSA as well as other societies, represent the state of medical science at the time of writing. Only high-quality, prospective, controlled clinical trial data demonstrating both benefit and safety will be sufficient to change the current recommendations (Lantos et al., 2010).

After reviewing the evidence, the panel presented the following conclusions regarding antibiotic therapy for patients with chronic symptoms after recommended treatment regimens for Lyme disease (Lantos et al., 2010):

- The prospective, controlled clinical trials for extended antibiotic treatment of Lyme disease have demonstrated considerable risk of harm, including potentially life-threatening adverse events.
- Prospective, controlled clinical trials have demonstrated little benefit from prolonged antibiotic therapy.
- The risk/benefit ratio from prolonged antibiotic therapy strongly discourages prolonged antibiotic courses for Lyme disease.

The International Lyme and Associated Diseases Society (ILADS) has published updated evidence-based guidelines for the management of Lyme disease that differ from many other organizations. (Cameron et al., 2014).

Additionally, a study published (Marzac et al., 2017) in the MMWR by the CDC highlights the severity and scope of adverse effects that can be caused using unproven treatments for chronic Lyme disease. The authors concluded systematic investigations would be useful to understand the scope and consequences of adverse effects resulting from treatment of persons with a diagnosis of chronic Lyme disease. Data sources to consider include clinician surveys, administrative claims databases, or implementation of state or local reporting systems for adverse outcomes related to these treatments.

Billing/Coding Information

CPT CODES

96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	; each additional hour (List separately in addition to code for primary procedure)
96367	; additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)
96368	; concurrent infusion (List separately in addition to code for primary procedure)
96372	Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

HCPCS CODES

J0456	Injection, azithromycin, 500 mg
J0696	Injection, ceftriaxone sodium, per 250 mg
J0698	Injection, cefotaxime sodium, per gm
J2540	Injection, penicillin G potassium, up to 600,000 units [IV]
S9494	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem (do not use this code with home infusion codes for hourly dosing schedules S9497-S9504)
S9497	Home infusion therapy, antibiotic, antiviral, or antifungal therapy; once every 3 hours; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9500	; once every 24 hours
S9501	; once every 12 hours
S9502	; once every 8 hours
S9503	; once every 6 hours
S9504	; once every 4 hours
J0558	Injection, penicillin G benzathine and penicillin G procaine, 100,000 units
J0561	Injection, penicillin G benzathine, 100,000 units
J0690	Injection, cefazolin sodium, 500 mg
J0743	Injection, cilastatin sodium; imipenem, per 250 mg
J1267	Injection, doripenem, 10 mg

J1335	Injection, ertapenem sodium, 500 mg
J1450	Injection, fluconazole, 200 mg
J1956	Injection, levofloxacin, 250 mg
J2185	Injection, meropenem, 100 mg
J2280	Injection, moxifloxacin, 100 mg
J2510	Injection, penicillin G procaine, aqueous, up to 600,000 units

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IV Antibiotic therapy for Lyme Disease, continued

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MEDICAL POLICY

VISCOSUPPLEMENTATION

Policy # 188

Implementation Date:7/5/00

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Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Intra-articular injections of sodium hyaluronate (HA), the sodium salt of HA, and Hylan GF-20 have been demonstrated to improve both symptoms (e.g., pain) and function associated with osteoarthritis (OA) of the knee. Osteoarthritis is characterized by degenerative loss of articular cartilage, sub-chondral bony sclerosis, and cartilage and bone proliferation at the joint margins with subsequent osteophyte formation.

HA plays a major role in the maintenance of the structural and functional characteristics of the extracellular matrix of the cartilage and of the synovial fluid. The unique viscoelastic quality of synovial fluid is essential for proper lubrication of the joint surface, which, together with the articular cartilage, allows smooth motion of the joint without friction or inflammation. In addition, HA has been shown to play a role in the regulation of cellular activities and may have an anti-inflammatory effect as well. Thus, intra-articular injection of sodium hyaluronate ("viscosupplementation"), may act to restore the lubricating properties of synovial fluid and promote healing of the articular cartilage. Hyaluronate is also thought to have direct analgesic effects, which may account for some of the pain relief associated with its use in arthritic joints. The currently approved HA products in the U.S. are: Euflexxa, Durolane, Gel-One, Gelsyn-3, Hyalgan, Hymovis, Monovisc, Orthovisc, Synvisc-One, Synvisc, Supartz Fx, TriVisc, GenVisc, SynoJoynt, and VISCO-3.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health does NOT cover viscosupplementation for any other joint except for the knee, including but not limited to: TMJ, shoulder, elbow, wrist, hip, and ankle. This meets the plan's definition of investigational/experimental.

Select Health covers viscosupplementation of the knee, if the patient has a positive response (i.e., documented pain reduction and improved function) persisting for at least 3 months after completion of the first course of therapy.

Patients must meet ALL the following indications:

1. Patient is between the ages of 40–65 years**
2. Patient has documented, primary osteoarthrosis deformans (i.e., osteoarthritis) of the knee that has been confirmed radiographically (by an orthopedist, rheumatologist, physical medicine and rehabilitation, pain management specialist, sports medicine physician, or radiologist)

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3. Patient has both:
   a) "MODERATE" anatomic disease as reported as radiologic grade II or III disease or "moderate" to "moderate-severe diagnosis" (not grade I or IV and not "mild" or "severe" diagnosis), AND
   b) "MODERATE" to "SEVERE" functional impairment (see below) of the knee due to OA
4. Patient has failed all the following more conservative therapies, or such therapies are not tolerated or are contraindicated:
   a) Weight reduction efforts
   b) Activity modification and/or physical therapy
   c) OTC analgesics
   d) NSAIDS (at least a 1-month trial during the past 3 months)
   e) Intra-articular steroid injection (at least 1 trial within the past 6 months)
5. Failure of one preferred viscosupplement: Synvisc, Synvisc-One, or Euflexxa (Please note: the preferred agents do not require prior authorization when administered with a diagnosis of osteoarthritis of the knee).
6. The treating provider does not anticipate a total knee replacement within the next 6 months.
7. Subsequent injections must be reauthorized every 6 months, complete with chart notes documenting response to previous treatment.
8. The viscosupplementation product must be FDA approved.

Special considerations

**Patients outside of listed age range, if the patient is not a candidate for total knee replacement, will be considered on a case-by-case basis.

Grading of Functional Impairment

Mild	Moderate	Severe
1. Discomfort but rare functional limitation. 2. Episodic flares.	1. Some functional limitation and reduced mobility. 2. Regular flares requiring constant analgesic or NSAID use.	1. Poor mobility and near constant pain. 2. Frequent or perpetual flares requiring treatment.

Quantity limit per treatment:

Product Name	Number of Injections	Course of Treatment
Euflexxa	3	3 weeks
Durolane	1	1-time administration
Gel-One	1	1-time administration
Gelsyn-3	3	3 weeks
Hyalgan	5	5 weeks
Hymovis	1	1-time administration
Monovisc	1	1-time administration
Orthovisc	4	4 weeks
SynoJoynt	3	3 weeks
Synvisc-One	1	1-time administration
Synvisc	3	3 weeks
Supartz Fx	5	5 weeks
TriVisc	3	3 weeks
Triluron	3	3 weeks
GenVisc	5	5 weeks
VISCO-3	3	3 weeks

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

A 2004 Hayes review concluded the following about injection of sodium hyaluronate for osteoarthritis: "There is evidence from a number of randomized, double-blind, placebo-controlled clinical trials that intra-articular HA can relieve pain and allow increased activity in patients with OA of the knee, as well as for those with disc disorders and OA of the TMJ who have failed or cannot tolerate conservative therapy. The treatment effect is similar in magnitude to that provided by corticosteroids, suggesting that use of HA should be reserved for patients who have failed steroid therapy or in whom steroid therapy might be contraindicated. While the evidence supporting the beneficial effect of a single course of treatment with HA is strong, there is presently limited information regarding the long-term benefits or adverse effects of repeated treatments, and there is only preliminary evidence suggesting that HA may also have disease-modifying effects. Therefore, a Hayes Rating of 'B' is assigned for a single course of treatment for patients with OA of the knee and for patients with OA or disc displacement of the TMJ, with the goal of providing symptomatic relief. This Rating assumes that the patient has significant pain and/or disability associated with OA, has failed conservative therapy, including physical therapy, exercise, occlusal alignment, bite plates, nonprescription analgesics, and that intra-articular corticosteroids have either been ineffective or are contraindicated."

Three systematic reviews evaluated low- versus high-MW HA. Lo et al.'s meta-analysis evaluated 22 trials and concluded that the pooled effect size for HA was 0.32 relative to placebo. With the exclusion of 2 Synvisc trials, which reported an effect size > 1.5, the pooled effect size for HA decreased to 0.19. A meta-analysis by Wang et al. evaluated 20 trials and reported that high-MW HA (Synvisc) trials had much greater pooled mean differences versus low-MW HA trials. The largest and most extensive evaluation of the HA products was performed recently by Bellamy et al. as a Cochrane Review. Because of differences in MW, concentration, treatment schedules, and mode of production, this review evaluated each product independently and concluded that HA injections are effective, though relative effectiveness within the class could not be determined. Each of these meta-analyses concluded that HA has a modest effect versus placebo for the treatment of OA of the knee. However, excess heterogeneity between the HA studies limited the authors from making definitive conclusions about the possibility of increased efficacy with the use of higher-MW HA.

Given the indeterminate findings of the systematic reviews of meta-analyses, one must turn to the primary literature which also has limited evidence for any difference between high molecular weight and low molecular weight products. Two randomized controlled trials, Wobig et al. and Raman et al., suggest that high-MW HA may be more efficacious than low-MW HA. The robust effect noted in the Raman study may have been related, in part, to the unexplained omission of two study groups from statistical analyses: the denatured Synvisc control group and another low-MW HA, Healon. The Raman study is only available in abstract form which makes the results difficult to evaluate and generalize to the HA class.

Confounding any conclusions regarding comparable effectiveness are the presence of two randomized clinical trials which have concluded that there is no clinical difference between high- and low-MW HAs for the treatment of OA of the knee. These trials, Karatosun et al. and Kotevoglu et al., are difficult to

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generalize to the HA class because in the Karatosun et al. study the Hospital for Special Surgery (HSS) pain score was used, rather than the standardized WOMAC pain index used in most of the HA trials and in the Kotevoglu study the difference in rescue medication usage between the groups was not reported, despite the fact that acetaminophen was permitted up to 4 g/day.

Finally, a non-inferiority trial conducted by Kirchner et al. compared the safety and efficacy of a high-MW HA produced by biological fermentation, Euflexxa, to that of a high-MW HA produced by cross-linking, Synvisc. There were no significant differences between the improvement in average WOMAC pain score between the groups, meeting the prospective criteria for non-inferiority. Patients using Euflexxa reported greater global satisfaction and less acetaminophen rescue and had fewer joint effusions (1 vs. 15), relative to the Synvisc group. The authors concluded that fermentation HA can reduce pain and improve function in patients with knee OA without the local reactions associated with cross-linked HA products.

There is no solid evidence to date from which to conclude that there is a clinical difference between the high- and low-MW HA products for the treatment of OA of the knee. Guidelines from the American Academy of Rheumatology support this conclusion, stating that: "Differences in clinical efficacy between the HA preparations as a function of molecular weight have not been demonstrated and there is no evidence that this has changed."

There are currently no prospective controlled studies directly comparing the efficacy of different HA products for repeat treatment of OA of the knee. However, based on the individual open-label analyses that have been completed, the FDA permitted the precaution stating that: "The safety and efficacy of repeat treatment have not been evaluated …" to be removed from the package inserts for Hyalgan and Synvisc.

The FDA's actions were supported in Jubb et al., which demonstrated that while the effect on pain was modest overall, the results represented an incremental improvement above oral pain medication.

Questions of duration between injections are described in the pivotal trials described in the package inserts for each HA product revealed differences between the products in terms of the studied duration of pain relief with a single course of treatment. Treatment with 5 injections of Supartz and Hyalgan, 4 injections of Orthovisc and 3 injections of Synvisc have been shown to provide pain relief for up to 6 months in patients who respond to the initial course of therapy. The only published trials currently available for Euflexxa report pain relief for up to 3 months following a single course of therapy. Medina et al. conducted a meta-analysis of seven HA studies and concluded that HA may provide short-term relief of pain and improved functionality for patients with OA of the knee, but effects do not persist beyond 6 months.

The available literature suggests repeat injections are likely safe and effective for the treatment of knee OA. The data also suggest that repeat treatment with the cross-linked, high-MW HA, Synvisc, may be associated with an increase in local inflammatory reactions. Except for Euflexxa, each of the available HA products have been shown to provide pain relief for up to six months, following an initial course of therapy. A 6-month duration of efficacy is further supported by the meta-analysis by Medina et al.

Billing/Coding Information
Covered: For the conditions outlined above

CPT CODES

20610	Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); without ultrasound guidance
20611	Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); with ultrasound guidance, with permanent recording and reporting

HCPCS CODES

J3490	Unclassified drug
J7318	Hyaluronan or derivative, Durolane, for intra-articular injection, 1 mg
J7320	Hyaluronan or derivative, GenVisc 850, for intra-articular injection, 1 mg

J7321	Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose
J7322	Hyaluronan or derivative, Hymovis, for intra-articular injection, 1 mg
J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose
J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose
J7325	Hyaluronan or derivative, Synvisc or Synvisc-One, for intra-articular injection, 1 mg
J7326	Hyaluronan or derivative, gel-one, for intra-articular injection, per dose
J7327	Hyaluronan or derivative, Monovisc, for intra-articular injection, per dose
J7328	Hyaluronan or derivative, Gel-Syn, for intra-articular injection, 0.1 mg
J7329	Hyaluronan or derivative, Trivisc, for intra-articular injection, 1 mg
J7331	Hyaluronan or derivative, SYNOJOYNT, for intra-articular injection, 1 mg
J7332	Hyaluronan or derivative, Triluron, for intra-articular injection, 1 mg

Revision History

Revision Date	Summary of Changes
10/12/23	For Commercial Plan Policy, removed previous criterion #5, which required only certain providers administer this treatment.
2/8/24	For Commercial Plan Policy, added new coverage criteria #5: "Failure of one preferred viscosupplement: Synvisc, Synvisc-One, or Euflexxa (Please note: the preferred agents do not require prior authorization when administered with a diagnosis of osteoarthritis of the knee)."
2/4/25	For Commercial Plan Policy, added SynoJoynt as an eligible viscosupplementation treatment option when criteria are met.

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