Coverage of any drug intervention discussed in the plans prior authorization guideline is subject to the limitations and exclusions outlined in the member's benefit certificate or policy and to applicable state and/or federal laws.

☒ **Commercial (Small & Large Group)** ☒ **ASO** ☒ **Exchange/ACA**
☐ **Medicare Advantage (MAPD)**

Intravenous Ketamine for Chronic Pain and Mental Health and Substance Related Disorders MB2300

Covered Service: NO

Prior Authorization Required: NO

Additional Information: Prescribed by (or in consultation with) pain specialists with prior authorization through The Plan Pharmacy Services.

Medicare Policy: Prior authorization is not required for Medicare Cost products (Dean Care Gold) and Medicare Supplement (Select) when this drug is provided by participating providers. Prior authorization is required if a member has Medicare primary and the plan secondary coverage. This policy is not applicable to our Medicare Replacement products.

Wisconsin Medicaid Policy Coverage of prescription drug benefits is administered by the Wisconsin Medicaid program. Coverage of medical drug benefits is administered by the Wisconsin Medicaid fee-for-service program. Medical drugs not paid on a fee-for-service basis by the Wisconsin Medicaid program are covered by the plan with no PA required.

1.0 FDA Indication

1.1 Ketamine

1.1.1 Ketamine hydrochloride injection is FDA-approved for the induction of anesthesia prior to the administration of other general anesthetic agents, and to supplement low-potency agents, such as nitrous oxide, for procedural sedation. IV ketamine for the treatment of chronic pain or symptoms of all mental health (including major depressive disorder, obsessive compulsive disorder, suicidal cognition, and post-traumatic stress syndrome) and substance-related disorders is an off-label use.

1.2 Treatment Guidelines/Consensus statements:

1.2.1 American Society of Regional Anesthesia and Pain Medicine – Joint Consensus Guideline (2018) – IV Ketamine for Chronic Pain

1.2.1.1 Weak evidence supporting use of IV ketamine for short-term improvement in patients with spinal cord injury pain

1.2.1.2 Moderate evidence supporting use of IV ketamine for improvement in patients with complex regional pain syndrome (CRPS) up to 12 weeks

1.2.1.3 Weak or no evidence for immediate improvement for other pain conditions, including mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache, and spinal pain

1.2.2 American Psychiatric Association (APA) – Consensus Guideline (2017) – IV Ketamine for mood disorders

1.2.2.1 Available studies had relatively small sample sizes, did not evaluate the longer-term efficacy of ketamine, and provided limited data on safety.

1.2.2.2 Clinicians must consider the limitations of available data and potential risks associated with ketamine treatment, including suicidal ideation and potential for substance abuse.

2.0 Policy / Criteria:

2.1 IV Ketamine is considered not covered due to insufficient evidence to demonstrate long-term clinical efficacy and safety for treatment of chronic pain

2.1.1 Two trials with a total of 100 patients provide limited evidence that courses of IV ketamine may provide temporary relief (2 to 4 weeks) to some chronic pain patients in some settings. Neither of the RCTs used an active control, raising concerns about placebo effects.

2.1.2 A phase 2 study investigated use of anesthetic dosing of ketamine in 20 patients with refractory CRPS. Symptoms were either long standing(range, 6-68 months), spreading, or rapidly progressive, and refractory to conventional nonmedical (physical therapy, psychological approaches), or pharmacologic (mono- or combined therapy) and interventional treatments (at least 3) including selective nerve blocks, epidural analgesia, brachial plexus blocks, sympathetic ganglion blocks, intravenous regional sympathetic blocks, spinal cord stimulation, surgical sympathectomy, or intrathecal drug delivery systems. Patients were intubated and mechanically ventilated (except for the first 3 patients). Ketamine infusion was titrated up to a dose of 7 mg/kg/h with infusion over 5 days, and then tapered downward until consciousness was attained. Midazolam was co-administered to a level of deep sedation to attenuate agitation and other AEs. Outcomes were assessed at 1 week and 1, 3, and 6 months after treatment. Pain intensity decreased from a numeric rating scale of 9 at baseline to 0.5 at1 week and remained low (2.0) at 6 months. Three patients relapsed but with lower pain (3.8) than at baseline.

Pain relief was 94%, 89%, and 79% at 1, 3, and 6 months, respectively. Upper- and lower-extremity movement improved from 3.2 at baseline to 0.4 at 6 months for arm movement and from 2.3 a baseline to 0.6 at 6 months for walking. At 6 months, there was a significant difference in the ability to perform activities of daily living; 1 patient rated total impairment; 3, severe impairment; 6, moderate impairment; and 10 patients, no impairment. Impairment in the ability to work was rated at baseline as complete by 11, severe by 5, and moderate by 4 patients. At 6 months, 2 patients remained unable to work, 4 had moderate impairment, and 14 patients reported no impairment. Psychotropic AEs resolved in the first week in most patients, although 5 patients reported difficulties with sleeping and recurring nightmares for 1 month following treatment. Muscle weakness was reported in all patients for up to 4 to 6 weeks' post treatment. As indicated by the authors, a strong placebo response to this intensive intervention was expected, and a large, multicenter RCT would be needed to definitively establish efficacy and safety. At this time, the beneficial effect of IV administration of ketamine is considered suggestive but not proven; additional trials are needed.

2.2 IV Ketamine is considered not covered due to insufficient evidence to demonstrate long-term clinical efficacy and safety for treatment of symptoms of all mental health (including major depressive disorder, obsessive compulsive disorder, suicidal cognition, and post-traumatic stress syndrome) and substance-related disorders.

2.2.1 Small randomized, controlled trials have demonstrated efficacy of ketamine in producing significant improvement in depressive symptoms in the short-term with effects generally lasting days or weeks. However, the long-term safety and efficacy with prolonged use of this medication, and the effects of repeated treatments have not been clinically evaluated.

2.2.2 Acute benefit of ketamine is only short lived and can produce psychotomimetic effects. Because of this, the APA recommends not to use ketamine/esketamine in patients with previous psychotic symptoms.

2.2.3 Ketamine is also potentially neurotoxic, particularly with longer-term administration.

2.2.4 Following a successful course of treatment with ketamine or electroconvulsive therapy, relapse is nearly two times greater with ketamine.

3.0 Policy Rationale

3.1 The intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of IV ketamine for chronic pain or mental health and substance-related disorders.

3.2 Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV ketamine for chronic pain or mental health and substance-related disorders.

3.3 The evidence is insufficient to determine that IV ketamine results in an improvement in the net health outcome.

Comment(s):

1.0 *Codes and descriptors listed in this document are provided for informational purposes only and may not be all inclusive or current. Listing of a code in this drug policy does not imply that the service described by the code is a covered or non-covered service. Benefit coverage for any service is determined by the member's policy of health coverage with the plan. Inclusion of a code in the table does not imply any right to reimbursement or guarantee claim payment. Other drug or medical policies may also apply.

1.1 NDC and HCPCS codes

Medication Name		How Supplied	National Drug Code (NDC)	HCPCS code
Brand	Generic			
Ketamine	Ketamine	Various	Numerous	J3490

	Committee/Source	Date(s)
Document Created:	Medical Policy Committee/Health Services Division/Pharmacy Services	February 15, 2023
Revised:	Medical Policy Committee/Health Services Division/Pharmacy Services	
Reviewed:	Medical Policy Committee/Health Services Division/Pharmacy Services	February 15, 2023

Effective: 06/01/2023
Published: 06/01/2023

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