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The Honorable Seema Verma
Administrator
Centers for Medicare & Medicaid Services
US Department of Health and Human Services
200 Independence Avenue SW
Washington, DC 20201

Dear Administrator Verma,

I write to request your urgent reconsideration of the Centers for Medicare & Medicaid Services (CMS) non-coverage determination (NCD) of home use of oxygen therapy for acute treatment of cluster headache (CAG-00296R).

Cluster headache is widely recognized as one of the most severely painful disorders known. Approximately 500,000 people in the US may experience cluster headache, where pain occurs in abrupt and agonizing attacks, in cyclical patterns that can last for weeks to months. Fifteen percent of people with cluster headache experience attacks of excruciating pain every day.

High flow rate 100% oxygen therapy provides critical relief from the acute pain of cluster headache so that patients can regain quality of life. Oxygen therapy for the treatment of cluster headache is effective within minutes. This is a crucial therapeutic benefit for a condition where recurrent individual attacks often reach extreme pain levels within seconds. It is the only reliable, safe, and effective acute therapy available for individuals living with cluster headache.

I have both personal and professional familiarity with this specific medical issue. I have experienced the excruciating pain of cluster headache attacks and I can attest to the extraordinary effectiveness, rapidity, and reliability of oxygen therapy for their relief. Moreover, as a practicing anesthesiologist, and past Chief of Obstetric Anesthesiology at the Johns Hopkins Hospital, I am highly familiar with the detailed benefits and risks of medical gas therapies, including those for oxygen. I am confident that high flow 100% oxygen therapy is safe for use at home by Medicare beneficiaries for the acute treatment of cluster headache attacks.

Oxygen therapy has been an undisputed first line agent for acute treatment for cluster headache attacks, since it was first reported in 1952. This medical consensus is supported by broad clinical experience and by controlled clinical trial research data that support its efficacy and safety, including enrolled subjects up to 70 years of age (Cohen et al. *JAMA*. 2009;302:2451-2457.). There are no published clinical trial reports or case reports, whatsoever, of any serious adverse events or serious side effects of use oxygen therapy for cluster headache in patients of any age group. As a consequence, oxygen therapy is cited as the standard of care in the practice guidelines and texts for cluster headache therapy of the National Institutes of Health, Agency for Healthcare Research Quality, American Headache Society, American Academy of Neurology, Health Resources & Services Administration, European Federation of Neurological Societies, National Headache Foundation, and the Institute for Clinical Systems Improvement. The Veterans Administration covers home oxygen therapy for its beneficiaries with cluster headache.

As a result of the NCD, Medicare and Medicaid covered cluster headache patients often receive unnecessary, costly, and typically ineffective, emergency department services and hospital admissions. The duration of cluster headache attacks (mean approximately one hour, maximum three hours) makes this treatment impractical in emergency departments; attacks often end before patients can reach hospital-based treatment. Furthermore, the common nocturnal timing of attacks, and their frequency (i.e. often multiple times per day, every day, for weeks) makes emergency department treatment infeasible.

There is no safe and effective alternative to oxygen therapy for many Medicare eligible cluster headache patients. Available alternative acute therapies carry clear and serious risks. While 6mg subcutaneous sumatriptan is an FDA-approved treatment for this cluster headache indication, it is not proven safe for use more than twice per day, or daily for weeks on end. Cluster headache attacks may occur up to eight times per day. CMS also limits availability of sumatriptan, often to no more than 10 treatments per month. Sumatriptan is contraindicated in the setting of cardiovascular ischemic risks or stroke which are prevalent among Medicare eligible patients.

Lack of availability of home oxygen therapy has led to prescription of opioids for cluster headache patients resulting in adverse outcomes. Opioid medications are typically ineffective for this disorder, but carry established risks of dependency, abuse, and addiction. The lack of availability of home oxygen for relief from excruciating cluster headache attacks may also lead to patient self-harm; cluster headache is associated with a 20-fold increased risk of suicide. Finally, further financial hardship may fall to low-income Medicare or Medicaid beneficiaries if they have been prescribed home oxygen for cluster headache, but must pay for this out of pocket due to the NCD.

The NCD cites potential safety risks for home use of oxygen for cluster headache that are not necessarily relevant in this setting. For example, the NCD cites a "risk of suppression of the hypoxic drive to breathe" in unsupervised COPD patients receiving oxygen therapy. However, such hypothetical effects are usually associated with prolonged oxygen exposures not seen with cluster headache treatment. And, of course, oxygen is only available by prescription and the prescriber would take co-existing diseases into account. Oxygen therapy when delivered, as indicated, for cluster headache attacks is only deployed for a maximum of 20 minutes at a time, as needed, typically once or twice daily, and up to a maximum of 8 times per day.

The NCD also cites oxygen therapy as leading to risks of significant tissue damage, such as "blindness and pulmonary fibrosis". Yet the NCD again cites publications stating that "the first signs of toxicity appear after 10 hours of oxygen at 1 ATA [atmosphere]" (Tinits, P, *Ann Emerg Med*. 1983;12:321) and that "100% oxygen can be tolerated at sea level for about 24-48 hours without any serious tissue damage" (Patel et al, *Journal Indian Academy of Clinical Medicine*, 2003; 4:234). This latter publication further mentions toxicity risks from prolonged oxygen that are certainly irrelevant to Medicare beneficiaries, such as blindness from retrolental fibroplasia (almost exclusively reported in premature infants) or deafness from dysbaric osteonecrosis (almost exclusively reported in astronauts in space). These remote potential risks of oxygen therapy cited in the NCD should certainly not weigh against the manifest relief from recurrent excruciating pain.

Current CMS Guidelines for Home Oxygen Therapy (ICN 908804; October 2016) do, in fact, appear to already cover home use of oxygen for cluster headache, though this is not recognized by CMS. That is, CMS covers home use of oxygen in the setting of "morning headaches", if these symptoms are deemed to be "hypoxia-related". This clinical indication is directly comparable to cluster headache. That is, cluster headache attacks often occur with nocturnal timing, awakening patients from sleep (i.e. "morning headaches"). Cluster headache is also strongly linked to hypoxic mechanisms. Apart from cluster headache attacks being relieved by high-flow 100% oxygen, sleep apnea is associated with hypoxia and has a greater than 8-fold higher prevalence among cluster headache patients.

Prior to granting CMS coverage of home oxygen for cluster headache, the NCD mandated that an approved prospective clinical study be performed to prove the safety of this therapy in a cohort of Medicare eligible patients (Coverage with Study Participation (CSP) form of Coverage with Evidence Development (CED)). This demand presents multiple, likely insurmountable, challenges. Prevalence estimates indicate that fewer than 50,000 Americans with cluster headache are 65 years or older (i.e. Medicare eligible). The NCD also mandates that adequate safety assessments be performed in particular patient subgroups of that elderly population. Specifically these subgroups include racial, sex, sexual orientation, ethnic, and socio-economic

demographics. Further, for validity, study subjects would likely be excluded from the trial if they had previously received oxygen therapy for cluster headache. A valid trial would also exclude subjects that had significant cardiovascular risks (common among Medicare eligible patients) since this would contra-indicate the use of subcutaneous sumatriptan, either as rescue therapy or as a positive treatment control arm. It would be unethical to include a placebo arm in the proposed trial given the availability of a therapy with proven efficacy (i.e. sumatriptan) for these severely painful attacks. Moreover, subjects in this study would need to live sufficiently close to investigator study sites for appropriate study follow-up visits, either scheduled or possibly emergent. This proposed large, diverse, elderly study cohort would then need to be followed longitudinally for possibly ten years of participation to generate meaningful long-term safety results. In other words, it would be essentially impossible to identify and recruit study subjects in sufficient quantity and for sufficient duration for the required study to be successfully executed. Finally, such a safety trial would also likely be exorbitantly expensive to undertake, with no obvious funding mechanism in sight. Did CMS require a similar prospective safety trial before coverage of home oxygen was granted to Medicare beneficiaries with "hypoxia-related" "morning headaches"?

Since 2010, leaders of the American Headache Society, the American Academy of Neurology, the Alliance for Headache Disorders Advocacy, and Clusterbusters (the national cluster headache patient advocacy organization) have appealed to CMS on multiple occasions to instate coverage of home oxygen use for cluster headache. These appeals were uniformly denied.

In May 2014, a number of my US congressional colleagues (Senators Coons, Johaans, Inhofe, Durbin, Fischer, Tester, Ayotte, Warren, Markey, Merkley, Manchin, Pryor, Casey, Carper, Shaheen, and Representative Eshoo) also wrote to then-CMS Administrator Marilyn Tavenner to appeal the NCD. Her formal response to them from (6/24/14) was to continue the non-coverage policy, with her explanation limited to stating that "no clinical trials involving the home use of oxygen to treat CH have been approved by the Centers for Medicare & Medicaid Services".

On June 1st of last year, my Deputy Chief of Staff, Mr. Bryan Shuy, spoke directly with Dr. James Rollins (Director, Division of Items and Devices, Coverage and Analysis Group, CMS) about reversing the NCD. At that time, Dr. Rollins re-iterated the CMS requirement for new trial safety data. Subsequent to Mr Shuy's conversation with Dr. Rollins, new clinical data have, in fact, emerged that further strongly support reversal of the NCD.

Investigators at the University of West Georgia recently shared with me not-yet published retrospective survey data of patients diagnosed by physicians with cluster headache. Among 61 cluster headache patients aged 65 or older (mean age 70 years old, oldest 98 years old) who

had used oxygen therapy for cluster headache attacks (mean 2503 oxygen treatments per respondent lifetime), none had ever experienced any severe psychological, emotional, physical, or medical complications of oxygen therapy. Moreover, sixty four percent of these respondents reported oxygen to be either very or completely effective for acute treatment of cluster headache attacks.

In summary, it is the uniform consensus medical opinion that home use of oxygen for cluster headache is very safe and highly effective. This is beyond dispute. The value of this therapy is not in clinical equipoise. It is therefore unethical for CMS to continue to withhold coverage of this treatment from Medicare and Medicaid patients.

I respectfully request your urgent review and reversal of the anomalous and wholly unsupported NCD that denies coverage of home use of oxygen to treat cluster headache attacks among Medicare and Medicaid beneficiaries.

I would greatly appreciate your careful and timely attention to this request and response. I would welcome the opportunity to discuss this with you further.

Sincerely,

Andy Harris, M.D.

Member of Congress