5/7/20

To Whom It May Concern:

I am writing on behalf of my patient, X, to appeal the recent denial of Xyrem. I am requesting this appeal for three reasons:

1. Although her current MSLT-based diagnosis is idiopathic hypersomnia, it is very likely that her true underlying diagnosis is narcolepsy, for which Xyrem is FDA-approved.
2. ***She has been treated with Xyrem with important clinical benefit since at least 2012, and Xyrem is the only medication that has consistently benefitted her narcolepsy/hypersomnia symptoms***.
3. There are no FDA-approved medications for idiopathic hypersomnia, despite sleepiness equivalent to that seen in narcolepsy, and so denying effective medications for people with idiopathic hypersomnia because of lack of FDA approval leaves them with no treatment options.

These three issues are elaborated below:

1) Regarding X's diagnosis of idiopathic hypersomnia, it is important to understand that current diagnostic tools cannot reliably differentiate narcolepsy (type 2) from idiopathic hypersomnia, and so while her current diagnosis is technically idiopathic hypersomnia, it is likely that her true underlying disease is narcolepsy. The ***only*** clinical feature that currently differentiates idiopathic hypersomnia from narcolepsy without cataplexy is the presence of two or more sleep onset REM periods (SOREMPs) at polysomnography/multiple sleep latency test (*Heier MS et al, Sleep, 2007:30;969-73*). Unfortunately, SOREMPs are poorly reproducible on repeat testing, and people who initially are diagnosed with idiopathic hypersomnia are often subsequently found to have narcolepsy if they undergo repeat testing (*Trotti LM et al, Journal of Clinical Sleep Medicine, 2013;9(8):789-95; Coelho FM et al, J Clin Neurophysiol, 2011;28(4):412-4; Goldbart A et al, Sleep, 2014;37(6):1043-51*). However, repeat testing is time- and cost-intensive, and would require X to come off of beneficial medications, and so it is inappropriate to perform at this time. The inability of the MSLT to adequately distinguish idiopathic hypersomnia from narcolepsy has led experts in the field to conclude that the presence of two or more SOREMps do "... not appear to have any specific pathognomonic significance" (*Singh M et al, Sleep, 2006:29(7):890-895*).

Furthermore, data-driven cluster analysis has shown that patients with narcolepsy without cataplexy and those with idiopathic hypersomnia are sorted statistically into the *same* cluster – with the implication that the diseases are similar enough that they cannot

be reliably distinguished on clinical grounds either (*Sonka K et al, Sleep Medicine, 2015: 16(2):225-31*). Additionally, to the extent to which symptoms may suggest narcolepsy as opposed to idiopathic hypersomnia, X's symptoms are more suggestive of narcolepsy, including fragmented nocturnal sleep and refreshing daytime naps. For all of these reasons, ***I believe the most appropriate working diagnosis for X is narcolepsy***.

2) X has taken Xyrem with clinical benefit for seven years, while her symptoms have been refractory to multiple other medications. These include concerta, provigil, nuvigil, adderall (IR and XR), ritalin, strattera, carnitine, flumazenil, clarithromycin, plaquenil, gluten free diet, folinic acid, CPAP, zofran, mestinon, cytomel, and lamictal. In light of this, it is particularly notable that she does get symptomatic benefit—i.e., reduction in sleepiness severity—from Xyrem.

3) My understanding is that this medication is sometimes denied because idiopathic hypersomnia is not an FDA-approved indication for Xyrem. While I certainly understand the preference for using medications for their labelled uses, there are currently NO medications that are FDA-labelled for the treatment of idiopathic hypersomnia. Yet it is a recognized, in this case disabling, neurological disease. By limiting treatment to those diseases that are FDA labelled, you will remove ALL treatment options in X's case. Despite the absence of labelling, Xyrem is clinically as effective in patients with idiopathic hypersomnia as it is in patients with narcolepsy (Leu-Semenescu S et al, Sleep Med. 2016 Jan;17:38-44).

In light of all of the above, I respectfully request you overturn your denial of Xyrem in this challenging case, in which Xyrem is clearly medically necessary. Please do not hesitate to contact me if I can provide additional information.

7/30/2020

To Whom It May Concern:

I am again writing on behalf of my patient X regarding Anthem's denial of my prescription of Xyrem for her sleep disorders. X has been my patient since 2012. I am a clinical physician board-certified in both Sleep Medicine and Neurology, as well as a research physician at Y University, with a focus on central hypersomnias, including

narcolepsy and idiopathic hypersomnia (IH). Given my breadth of knowledge in these areas, I am uniquely qualified to make the best treatment recommendations for these sleep disorders.

I have reviewed the claims file which was recently sent to X, as well as the denial letters and the Evidence of Coverage booklet. According to the appeal denial letter dated June 11:

> "*The previous coverage decision is being upheld. The medication is considered not medically necessary as defined in the definition section of your Certificate of Coverage (benefits booklet).*
> *Your plan has re-reviewed your specific circumstances and health condition as documented in the grievance and medical records provided to us by your treating physician. The reviewer is a health plan Medical Director, an MD who is board certified and specializes in Neurology. It's her recommendation that we keep our previous coverage decision. Here's why: We did not receive or did not see certain information about the use of the drug requested by your doctor, for your condition excessive daytime sleep (Idiopathic Hypersomnia). Use of this drug (XYREM 500 MG/ML SOLUTION) may be considered for approval under your health plan benefits when used for a certain condition (narcolepsy with or without cataplexy). We did not receive or we did not see information that shows you have this condition. We may consider approval of this drug for your condition under your health plan benefits if we receive certain information that show this drug can help your condition (medical literature references of medical studies of this drug for your condition or recognized drug compendia). We based this decision on your health plan prior authorization criteria for this drug and your health plan Off Label Drug Use policy, which can be found with other information on your prescription drug benefit at www.anthem.com/pharmacyinformation*."

Anthem's "Medical Director Decision" provides only a very brief and limited "Internal MD Rationale," which clearly does not provide a sufficient rationale for a denial: "*Records reviewed; 43 yo w/ h/o Idiopathic Hypersomnia, Migraines, on Xyrem, denial upheld*."

Yet, the only "record" found in the "claims file" you sent to X is a single office visit note from my office from November 2019. The Medical Director's rationale also does not indicate that my appeal letter, or any of its referenced journal articles, were reviewed and considered, nor does it mention my extensive rationale for why X's most appropriate working diagnosis is narcolepsy type 2 (NT2).

For Anthem's further review, I am resending my 5/12/2020 appeal letter, 2020 office visit notes, and full text of several relevant journal articles.

Additionally, your unnamed Medical Director is alleged to specialize in Neurology only, not Sleep Medicine. Narcolepsy and idiopathic hypersomnia (IH) are both rare diseases. Given that, even many Sleep Medicine specialists have very limited experience with, and knowledge of, these complex disorders.

I have reviewed the "Evidence of Coverage" for X's specific plan, and I find that Xyrem is medically necessary according to the definition of medical necessity as stated in that document. As detailed in my prior letter of 05/12/2020, current diagnostic tools (including the MSLT) cannot reliably differentiate between IH and NT2, and cluster analysis indicates that these diseases are similar enough that they cannot reliably be distinguished on clinical grounds either. However, ***given X's complete clinical picture and constellation of chronic symptoms, narcolepsy type 2 is the most appropriate working diagnosis.*** I made this same statement in my 05/12/2020 letter.

Xyrem is medically appropriate, and "on-label" for NT2. "Off-label" treatment with Xyrem for IH is also medically supported by the literature, which shows that Xyrem is clinically as effective in patients with IH as it is in patients with narcolepsy. This is unsurprising given the significant clinical overlap as detailed above, and in my prior letter. Of particular note, as I further detailed in my 05/12/2020 letter, there are *no* FDA-approved medications for IH.

Further, the "Evidence of Coverage" states the following regarding Off-Label Drugs:

> "*When prescribed to a Member with a life-threatening or chronic and disabling condition or disease, benefits are provided for the following:*
>
> - *Off-label Drugs*
> - *Medically Necessary services associated with the administration of such a drug.*
>
> *An off-label drug is a drug prescribed for a use that is different from the use for which it was originally approved for marketing by the federal Food and Drug Administration*."

As my office visit notes indicate, X is disabled by her chronic neurologic sleep disorder. She has been receiving disability benefits from the Social Security Administration as well as both of her private disability insurers (A and B) since 2012.

I have also reviewed Anthem's Xyrem Approval Criteria, and I find that X should be approved based on that criteria as well. Of note, several of the references for this Approval Criteria are quite old (Wise et al; Sateia et al) or not relevant (Epstein et al; Kapur et al). As I have detailed above, and in my prior letter, X's most appropriate

diagnosis is narcolepsy type 2, as MSLT's and SOREMPs are no longer considered accurate to distinguish between IH and NT2. She has tried and failed modafinil, armodafinil, methylphenidate, Concerta, and dozens of other treatments. ***Xyrem is the only medication that has consistently benefitted her narcolepsy/hypersomnia symptoms***. Without it, she experiences significant worsening in her symptoms, and increased severity of her daytime sleepiness.

Performing an MWT to document improvement with Xyrem, during the ongoing COVID-19 pandemic, would expose X to unacceptable risk, especially given that we already know she experiences significant clinical improvements with Xyrem. Furthermore, while the MWT is a measure of the propensity to fall asleep, it fails to capture numerous aspects of the experience of excessive daytime sleepiness, including brain fog, cognitive dysfunction, etc, which contribute substantially to X's disease burden and functional limitations. Similarly, the Epworth, as a measure of propensity to fall asleep, does not capture her clinical improvements particularly well. Additionally, she has been taking and benefitting from Xyrem for many years, such that her pre-treatment, baseline Epworth is so outdated that it is no longer reliable for the current situation.

I am again asking that you approve my prescription of Xyrem for X's sleep disorders. Xyrem is clearly medically necessary. If necessary, I would be happy to discuss my medical opinion, as well as my treatment of X, with any of your medical reviewers. No one from Anthem has reached out to me.