Prader-Willi Syndrome Association (NZ) Incorporated

PROVIDING ADVOCACY, EDUCATION AND SUPPORT FOR NEW ZEALANDERS WITH PWS AND THEIR FAMILIES

Wednesday 2nd March 2022

Feedback: **Proposal on access criteria for two oral COVID-19 treatments**

The PWSA(NZ) has concerns around the eligibility criteria for access to the two anti-viral medications, Nirmatrelvir with ritonavir (Pfizer's oral antiviral), and Molnupiravir (Merck's oral antiviral), for the treatment of acute COVID-19 disease.

Although PWS itself does not appear to be a risk factor for more serious illness with Covid-19, we are aware of individuals with PWS who have died as a result of Covid-19 infection through our international network, and we know that some of our members with PWS are likely to be more vulnerable to serious illness with Covid-19 due to the higher than typical prevalence of comorbidities associated with PWS.

It is thought that the majority of individuals with PWS are not necessarily immune compromised unless they have been identified as having central adrenal insufficiency (the prevalence rate of which has been disputed in studies to date). Therefore, given that most people with PWS would be expected to have adequate immune responses and are also highly likely to be vaccinated, we feel that the following criterion would exclude some of our most vulnerable members from accessing treatment:

> **3.3 Patient is vaccinated* and has at least two of the following: Aged 65 years or over, Māori or any Pacific ethnicity, any comorbidity as listed below****

PWS is a complex condition with multiple associated health risks. These often lead to a shortened life expectancy [1,2,3], especially as a significant proportion of our adult PWS population did not have the advantages of early diagnosis or access to growth hormone therapy available to children with PWS today. Indeed, the New Zealand PWS Association is not aware of any adults living with PWS in New Zealand aged 65 years or over. It is also thought that premature ageing occurs in PWS [4,5] and therefore, the inclusion of being aged 65 years or over in the access criteria is not appropriate for the PWS population group.

Comorbidities

There is a heightened vulnerability towards obesity and hyperphagia-related premature mortality in PWS, with respiratory failure found to be the most common cause of death, followed by cardiac failure [1,2].

> "*Among the adults who died of respiratory causes, most presented restrictive ventilatory impairment, a known comorbidity in the PWS population [31]. In addition, other intrinsic features of PWS increase the risk of severe respiratory problems. Upper airway hypotonia and abnormal response to hypercapnia and hypoxia have been well-described in animal models and the PWS population [32, 33]. Comorbidities like obesity and scoliosis coupled with sleep-disordered breathing [19, 34,35,36,37] can result in exacerbations of these abnormalities and may increase the risk of death from respiratory causes. Respiratory-related deaths, as well as other causes of death, were often the result of an acute event in the context of multiple comorbidities."*
> Pacoricona Alfaro, D.L., Lemoine, P., Ehlinger, V. et al. [2]

Another study which assessed rates of comorbidities associated with obesity in a large PWS vs non-PWS cohort, found that across all age groups, compared to non-PWS subjects, individuals with PWS experience markedly higher rates of type II diabetes (T2D), cardiovascular disease (CVD), and sleep apnoea (SA). [6]

Numerous scientific papers list the comorbidities associated with Prader-Will syndrome. In a recent paper looking at risk factors for thrombosis, Butler et al [7] state:

> *Reports have suggested an important association between obesity and early death in adults with PWS [4]. Comorbidities that are commonly associated with obesity in PWS include respiratory problems (pulmonary embolism, respiratory failure, and pulmonary hypertension) and deep venous thrombosis [5,6,7,8,9].*

Crino et al [8] report:

> *Differently to what occurs in non-syndromic obesity, PWS subjects showed lower trunk-to-appendicular fat mass ratio and lower visceral adiposity. In line with these findings, a higher insulin sensitivity is generally reported in PWS patients when compared to a matched obese population.[16]*
> *Comorbidities commonly associated with severe weight excess in PWS include respiratory problems (pulmonary embolism, respiratory failure, pulmonary hypertension) and sleep disorders (obstructive sleep apnea), right heart dysfunction, myocardial infarction, arterial hypertension, steatohepatitis, gallstones, deep venous thromboses, and chronic leg edema.[10,12,53,56] Overall, respiratory and cardiac diseases account for 38% and 16% of deaths in these patients, respectively [57]. Taking into account the metabolic profile, hyperlipidemia is reported in about a third of the subjects.[58] PWS subjects show a high prevalence of altered glucose metabolism (24.4%), including type 2 diabetes mellitus (T2DM) with multiorgan failure, that appears more common in obese and adult subjects.[59] In this context, metabolic syndrome (MS) is a strong risk factor for T2DM, as well as for atherosclerotic cardiovascular disease, and MS might be potentially one of the mechanisms responsible for excessive mortality in PWS.*

Another study revealed through systematic screening that many health problems in adult patients with PWS may be undiagnosed. [9]

Respiratory Problems and Infants with PWS

As mentioned, individuals with PWS are at increased risk for respiratory problems [10], especially as a result of obesity.Ventilatory control responses to hypoxemia and hypercapnia are known to be altered in PWS. Infants with PWS are at increased risk due to hypotonia at birth and weak chest muscles. Central sleep apnoea is common in infants with PWS and other problems may include hypoventilation and respiratory failure [11]. Respiratory tract infections can significantly affect some children with PWS, particularly if they have sleep apnoea /sleep disordered breathing. The ability to cough effectively and clear airways is also affected by the degree of hypotonia.

These respiratory problems at birth usually improve as children grow stronger and with the benefit of growth hormone treatment that can begin from the age of 6 months. However, our youngest children with PWS may be at increased risk from Covid-19 and they are not eligible for vaccination. Young children with PWS will not meet the comorbidities criteria in Pharmac's proposed access criteria and will therefore only qualify for antiviral treatment if they are a specific ethnicity.

Atypical Symptoms of Illness

It should also be noted that patients with PWS who test positive for Covid-19 need to be assessed with caution. Serious illness can sometimes be difficult to detect and monitor in PWS due to body temperature irregularities and the possibilities of a high pain threshold or lack of vomiting. It may also be unlikely that a person with PWS has a reduction in appetite because they are feeling unwell. Therefore, individuals with PWS may not present with typical symptoms of Covid-19, such as fever, and the only indicators of illness may be subtle changes in appearance, sleep, anxiety or behaviour.

This is why all our members are eligible for the annual influenza vaccination, including those who are otherwise healthy.

Recommendation

We understand that a limited supply of antiviral medication has been ordered and we also know that otherwise healthy individuals with PWS may not be at increased risk for serious illness and will therefore not need prioritised access to these medicines.

However, some of our members will be at increased risk, but will not qualify under the proposed criteria. The proposed criteria present an equity issue.

We ask that Pharmac apply criteria that allow for assessed vulnerability, perhaps a category that considers multiple comorbidities. There should be an acceptable category for 'other proven health risks based on patient history'.

References

1. Butler MG, Manzardo AM, Heinemann J, Loker C, Loker J. **Causes of death in Prader-Willi syndrome: Prader-Willi Syndrome Association (USA) 40-year mortality survey.** *Genet Med*. 2017;19(6):635-642. doi:10.1038/gim.2016.178

2. Pacoricona Alfaro, D.L., Lemoine, P., Ehlinger, V. *et al.* **Causes of death in Prader-Willi syndrome: lessons from 11 years' experience of a national reference center.** *Orphanet J Rare Dis* **14,** 238 (2019). https://doi.org/10.1186/s13023-019-1214-2

3. **What is the mortality and morbidity associated with Prader-Willi syndrome (PWS)?** Ann Scheimann, MD, MBA Associate Professor, Department of Pediatrics, Section of Nutrition and Gastroenterology, Baylor College of Medicine and Johns Hopkins Medical Institution

4. Sinnema M, Schrander-Stumpel CT, Maaskant MA, Boer H, Curfs LM. **Aging in Prader-Willi syndrome: twelve persons over the age of 50 years.** Am J Med Genet A. 2012 Jun;158A(6):1326-36. doi: 10.1002/ajmg.a.35333. Epub 2012 May 14. PMID: 22585395.

5. Donze SH, Codd V, Damen L, Goedegebuure WJ, Denniff M, Samani NJ, van der Velden JAEM, Hokken-Koelega ACS. **Evidence for Accelerated Biological Aging in Young Adults with Prader-Willi Syndrome.** J Clin Endocrinol Metab. 2020 Jun 1;105(6):2053–9. doi: 10.1210/clinem/dgz180. PMID: 31689713; PMCID: PMC7150612.

6. Diane E J Stafford, MD, Justin W Li, BA, David Yin, BS, Michael M Yeh, MD, MPH, Shawn Czado, BS, Sina Aghsaei, MSc, Marissa Suh, MPH, Kevin Francis, BS, Shawn E McCandless, MD, SUN-595 **Comparative Comorbidity Burden Among Patients with Prader-Willi Syndrome: A Population-Level Cohort Study**, *Journal of the Endocrine Society*, Volume 4, Issue Supplement_1, April-May 2020,SUN-595

7. Butler MG, Oyetunji A, Manzardo AM. **Age Distribution, Comorbidities and Risk Factors for Thrombosis in Prader-Willi Syndrome**. *Genes (Basel)*. 2020;11(1):67. Published 2020 Jan 7. doi:10.3390/genes11010067

8. Crinò A, Fintini D, Bocchini S, Grugni G. **Obesity management in Prader-Willi syndrome: current perspectives.** *Diabetes Metab Syndr Obes*. 2018;11:579-593. Published 2018 Oct 4. doi:10.2147/DMSO.S141352

9. Pellikaan K, Rosenberg AGW, Kattentidt-Mouravieva AA, et al. **Missed Diagnoses and Health Problems in Adults With Prader-Willi Syndrome: Recommendations for Screening and Treatment.** *J Clin Endocrinol Metab*. 2020;105(12):e4671-e4687. doi:10.1210/clinem/dgaa621

10. Gillett ES, Perez IA. **Disorders of Sleep and Ventilatory Control in Prader-Willi Syndrome.** *Diseases*. 2016;4(3):23. Published 2016 Jul 8. doi:10.3390/diseases4030023

11. Tan HL, Urquhart DS. **Respiratory Complications in Children with Prader Willi Syndrome.** Paediatr Respir Rev. 2017 Mar;22:52-59. doi: 10.1016/j.prrv.2016.08.002. Epub 2016 Aug 10. PMID: 27839656.