Why is Xyrem (Sodium Oxybate) not PBS listed or TGA registered (approved)?

What is the PBS?

The **Pharmaceutical Benefits Scheme (PBS)** Schedule lists all of the medicines available to be dispensed to patients at a Government-subsidised price. The Schedule is part of the wider Pharmaceutical Benefits Scheme managed by the **Department of Health and Aged Care** and administered by **Services Australia**.

For a medication to be considered for the **PBS** it must first be registered with the **TGA**. Xyrem is not registered with the **TGA** therefore it can not be considered for the **PBS**.

What is the TGA?

The **Therapeutic Goods Administration (TGA)** is part of the **Australian Government Department of Health**, and is responsible for regulating therapeutic goods including prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products. Prescription medicines must be registered with the **TGA** to be included on the **Australian Register of Therapeutic Goods (ARTG)**.

Applications for prescription drugs require a 'sponsor'. The sponsor is responsible for applying to the **TGA** to have their therapeutic good included on the **ARTG**.

A sponsor is a person or company that does one or more of the following:

- *exports therapeutic goods from Australia*
- *imports therapeutic goods into Australia*
- *manufactures therapeutic goods for supply in Australia or elsewhere*
- *arranges for another party to import, export or manufacture therapeutic goods.*

The degree of assessment and regulation that prescription medications must undergo is rigorous and detailed. There are many steps that sponsors must take, including the payment of non-refundable fees, and they must also provide comprehensive safety, quality and efficacy data.

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Why is Xyrem not registered with the TGA?

The first phase of a TGA application is the 'pre-submission'. In 2018 UCB Australia made a pre-submission as the sponsor for Xyrem under the orphan drug program (orphan drug designations allow for a waiver of the TGA application and evaluation fees).

Go to the TGA website for more information on the orphan drug program and what qualifies for designation.

The TGA did not respond favourably to UCB's pre-submission and raised some issues that required a response. These issues are unfortunately not easy to overcome, so the application has not progressed. The main issues include;

The TGA believes that Xyrem does not meet the criteria for orphan drug designation.

Important note: Both the sponsors of Dexamphetamine, Modafinil and Armodafinil submitted Category 1 applications to register the indication of Narcolepsy. The TGA advised "Based on that, it is advisable and only fair that UCB also submits a Category 1 Application to register Xyrem in the treatment of Narcolepsy indication."

It is a TGA requirement for comparator studies that show significant benefit over existing treatments.

The TGA stated in their response,

"...a "head to head" trial assessing the superiority of UCB Xyrem over those already registered products for narcolepsy will be more appropriate in terms of clinical evidence to justify UCB's implicit claim, that the effective treatment of the other "possible symptoms" associated with narcolepsy, such as catalepsy and fragmented night-time sleep, can only be provided by Xyrem.", and, *"The TGA requires properly conducted and well-designed, randomised clinical trial with active arm, demonstrating that only Xyrem has proven therapeutic effect on cataplexy (a possible component of the narcolepsy) which is not effectively managed by other registered drugs for narcolepsy."*

UCB responded by explaining,

"Currently, none of the existing stimulant treatment options have any proven effects on cataplexy. As such, UCB believes that it would not be ethical to conduct a head-to-head trial with drugs which do not have a proven effect on a specific symptom, and it would be difficult to convince investigators to participate and recruit for such a trial."

Unfortunately, it was the TGA's view that Xyrem still did not meet the criteria for orphan drug designation. UCB requested the TGA consider the possibility of narrowing the orphan indication being sought to narcolepsy type 1 (narcolepsy with cataplexy), which is in line with their intended indication for registration. The TGA advised UCB that they could apply for Xyrem via a Category 1 application, which is extremely expensive (<AU$ 400,000) and is not refundable if the application is denied.

Summary

While it isn't entirely out of the question that a sponsor will ever attempt to register drugs for disorders of hypersomnolence with the TGA again, under the circumstances, it is highly likely that sponsors in future will apply for a very specific indication, ie: Narcolepsy with Cataplexy (Narcolepsy Type 1) only.