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OX640: Shaping the future of nasal powder epinephrine using the innovative amorphOX® platform

Orexo is breaking new ground in the area of anaphylaxis with OX640, an innovative nasal powder epinephrine product. In this interview, Robert Rönn, SVP and Head of Research and Development at Orexo, shares the OX640 clinical study results, why FDA approval is expected, and the far-reaching benefits for patients and prescribers.

Is there a need for a new anaphylaxis treatment?
Yes, anaphylaxis is a serious allergic reaction that progresses very quickly, and if it isn't treated, it can be fatal. It affects approximately 26 million adult Americans[1] which is why we set out to create a product that's rapidly acting and more reliable than current epinephrine formulations. As a needle-free alternative, OX640 is easier for everyone to use, especially patients with needle phobias.

Robert Rönn, SVP and Head of R&D, at Orexo

What did your OX640 clinical study show?
The study was a success. OX640 showed rapid and extensive absorption from the nasal powder formulations and provided proof of concept.

We carried out a comparative bioavailability study where we examined four different formulations and used an EpiPen® autoinjector as a reference product. Overall, OX640 provided a higher total epinephrine (adrenaline) exposure than the EpiPen®.

The C_{max} values, which measure how high the concentration is in the patient after the drug has been administered, were comparable with the EpiPen®.

The study also included measurement of pharmacodynamic parameters, including heart rate and blood pressure. These are seen as surrogate markers of effectiveness because we're unable to test in people actually in a state of anaphylaxis for ethical reasons. We were looking to see if OX640 increased heart rate and blood pressure in our healthy subjects, and we found that it did. We can extrapolate from this that patients in anaphylaxis would

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6324316/

experience the same effects. This is crucial because when patients go into anaphylaxis, their blood pressure may fall dangerously low as a result of their body releasing histamines. Rapid epinephrine absorption is vital for patients experiencing anaphylaxis because they can become seriously ill so quickly, and we know that allergic reactions often happen when people are out and about and may be nowhere near a hospital.

Why is the amorphOX® platform so effective?
AmorphOX® is a highly stable, powder-based drug delivery platform that dissolves rapidly, making it easy for a patient to absorb their medication extremely quickly. It works with different APIs and dosages, and it can be used for different administration routes. AmorphOX® is highly versatile, and OX640 along with our overdose medications, are just the start of what we're going to be able to develop with it.

Another significant benefit of amorphOX® is its stability. Epinephrine is an unstable compound, so it degrades easily. We have done comparative stabilities studies where we stored OX640 powder and EpiPen® for a year at 40°C. During that time, EpiPen® lost roughly 25 percent of the epinephrine and OX640 lost 1 percent. Even in a single day at the beach, the epinephrine in a patient's EpiPen® will start degrading, which is why autoinjectors are designed to be stored at room temperature. Patients need to feel confident that the drug they're carrying with them is fit for purpose as it could save their life. OX640 offers patients more security that they'll get the recommended dose when they need it.

As a powder-based product, OX640 can also withstand freezing temperatures of as low as at least minus 20°C, whereas liquids freeze at around minus 10 to 15°C. Most competitor products under development are based on liquid formulations, so we're confident that OX640 will provide significant advantages over these.

Does OX640 offer any environmental benefits?
In general, manufacturing and supply chains generate high amounts of waste and carbon emissions. Current epinephrine products have a shelf life of only 22-24 months. Long manufacturing and supply times mean patients often only have a year left to use their autoinjector when they collect it from the pharmacy before it expires. Annual replacements contribute to high environmental and financial costs as patients can't just throw them away, they have to be processed as clinical waste. There are policies around waste management that hospitals, pharmacies and community health clinics need to follow.

Across the market, it's not unusual for there to be manufacturing issues with autoinjectors that can lead to supply shortages. I know of a case only last week where a batch of autoinjectors were taken off the market because they were malfunctioning.

OX640 is a robust, reliable product with a long shelf life and it offers significant benefits for both patients, prescribers, and the environment.

What benefits does OX640 offer patients?
Needle phobia is much bigger than I initially thought. It affects so many patients, especially children. Recently, I attended an Advisory Committee meeting, where they were discussing

a competitor's liquid nasal adrenaline product. We heard families speaking about the impact that needle phobia has on their lives. It's made me realise the huge value a non-injectable product can give. It was a privilege to listen to parents as they talked about their experiences. One family talked about how they have to forcibly hold their young child down because they're so afraid of the needle. Another family confessed to having delayed giving the medication to their child, even when they recognised the symptoms, because of the level of their child's fear. Even teachers are reluctant to use the product because they're worried about doing something wrong. With a nasal product, people are likely to take it much sooner.

Another benefit for patients is that OX640 is less than half the size of an autoinjector and much easier to carry around. It's a pocket-sized product, so patients don't even need to take a bag out with them, they can just slip it in their jacket pocket, or a purse, making it much more likely they'll take it with them when they leave their home. We know that some patients don't carry their medication around with them at the moment because the autoinjectors are so bulky. Some patients don't even bother taking their autoinjector out of the pharmacy.

Note: product image is a prototype

As OX640 is so stable, it doesn't include any of the antioxidants or preservatives that are used in other formulations to extend the shelf life. This makes OX640 a much cleaner product. Some patients who suffer with multiple allergies can also react to the sulphites used in other adrenaline products and, depending on the severity, they may be advised against using an autoinjector. While this is relatively rare, it's much better for patients to be able to use a product that doesn't contain any chemical additives.

What are the next steps for OX640?
At the FDA Advisory Committee meeting, a significant majority voted in favour of recommending approval of our competitor's liquid nasal epinephrine product for use in adults and children. The outcome will definitely also give us tailwind in our journey to bringing OX640 to the market. We're already in talks with the FDA about our final development program and expect to be filing an NDA with them in 2025.

As Orexo's key therapeutic area is substance use disorders and mental illness, we're looking for a partner not only for continued clinical development but also for commercialization of the product globally. We own the global rights to OX640, so the potential market is expansive and lucrative. An ideal partner would have experience of meeting patients living with severe allergies and prescribers specializing in this field of practice, either regionally or globally.

I'm so proud of what our team has developed with OX640. Everyone has worked together to create this innovative product that is useful, sustainable, and easier for patients to use. It is

because we know OX640 has the power to transform lives that we're confident of its future success.

Written by Georgina Hoy

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About Orexo
Orexo develops improved pharmaceuticals and digital therapies addressing unmet needs within the growing space of substance use disorders and mental health. The products are commercialized by Orexo in the US or via partners worldwide. The main market today is the American market for buprenorphine/naloxone products, where Orexo commercializes its lead product ZUBSOLV® for treatment of opioid use disorder. Total net sales for 2022 amounted to SEK 624 million and the number of employees was 126. Orexo is listed on the Nasdaq Stockholm Main Market (ORX) and is available as ADRs on OTCQX (ORXOY) in the US. The company is headquartered in Uppsala, Sweden, where research and development activities are performed.

For more information about Orexo please visit, **www.orexo.com**. You can also follow Orexo on Twitter, @orexoabpubl, LinkedIn and YouTube.