PSIVIDA AND OPHTHALMIC DRUG DELIVERY

Here, Paul Ashton, PhD, President & Chief Executive Officer, pSivida, describes how much of the progress that has been made recently in the treatment of ophthalmic diseases can be ascribed to effective drug delivery systems, and outlines some of the delivery technologies and resulting products for which pSivida has been responsible. pSivida's new platform technology, Tethadur, for the sustained, long-term delivery of biologics in the eye, is also described.

The ophthalmic pharmaceutical market has been expanding at a truly remarkable pace with the potential for even faster growth in the next decade. This expansion has been driven by the development of innovative, effective therapeutics for common devastating diseases. Many of these diseases such as diabetic macular edema (DME) and wet age-related macular degeneration (AMD) once blinded hundreds of thousands of people but now treatments are available, slowing or halting the progression of the diseases. Other serious conditions such as dry AMD and retinitis pigmentosa (RP) remain the subjects of intensive research, and optimism is high that effective treatments for these conditions will soon be developed.

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The eye has traditionally been an extremely difficult target for drug delivery as the efficacy of the blood-eye barrier limits the therapeutic effectiveness of systemic drug delivery, particularly as the dosages required to overcome this barrier increase adverse side effects. The back of the eye where the retina is located is even more challenging for drug delivery, because it is inaccessible to eye drops used to treat front-of-the-eye diseases. Intraocular injections are now generally used to deliver therapeutics to the back of the eye but the repeated injections required (sometimes as frequently as every month) can have adverse consequences, most commonly intraocular infection. Further, both systemic dosing and intraocular injections face challenges in sustaining the appropriate concentrations of drug in the eye.

There are currently only two approved drug delivery systems capable of delivering drug to the eye on a sustained basis – pSivida's three Durasert™-based products and Allergan's Ozurdex®. Fortunately, more products designed to address the challenges and opportunities of retinal drug delivery are now under development.

pSivida is seeking to develop a series of new sustained release ophthalmic products based on its proprietary Durasert and Tethadur™ platform technology systems. These systems are designed to provide controlled release for periods of months to years for small drug molecules and biologics to treat eye disease.

pSivida's Durasert technology can be used to deliver different drugs for periods of months to years with a single application. The first generation of this technology is Vitrasert®, which delivers ganciclovir to treat CMV retinitis for over six

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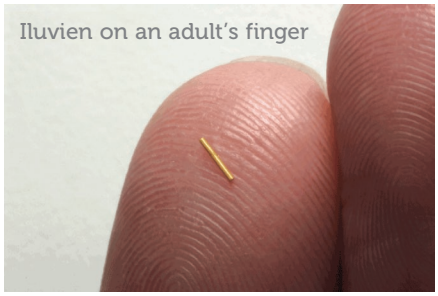

Figure 1: Iluvien®, pSivida's most recently approved iteration of Durasert technology.

months. Approved almost 20 years ago, this implant was partnered with Bausch + Lomb and was the first drug approved for retinal disease. pSivida developed a second generation of Durasert technology for Retisert®, the first therapeutic approved for the treatment of posterior uveitis (partnered with Bausch + Lomb and approved in 2005). This product, also an implant, delivers the corticosteroid fluocinoline acetonide (FA) and extended the duration of delivery to 30 months.

pSivida's most recently approved iteration of Durasert technology is Iluvien® (Figure 1), partnered with Alimera Sciences and approved in in the US in 2014 following EU approval in 2012. This product is injectable and delivers FA for three years. Iluvien was the fourth sustained delivery product approved by the US FDA for back-of-the-eye disease. The third was Allergan's Ozurdex® (dexamethasone in a PLGA matrix), approved in 2009.

Successive generations of Durasert products have lengthened the sustained release of the drugs they deliver and simplified the delivery of drugs to the back of the eye. With a single application, Vitrasert is effective for five to eight months, Retisert for 30 months and Iluvien for three years. While pSivida's first two products, Vitrasert and Retisert, are implanted into the eye in a surgical procedure, both Iluvien and Allergan's Ozurdex are injected in an office visit. Ozurdex is bioerodible, releasing more than 90% of its drug in the first month, but the pharmacodynamics effect is longer, up to six months in some cases.

pSivida is developing Durasert-based devices that provide long-term sustained release from a bioerodible system as, one would assume, are Allergan and others.

Durasert and Ozurdex technologies will not be capable of delivering all ophthalmic therapeutics for all applications. For example, sustained release of water-soluble drugs will likely be difficult from matrices like

Figure 2: In diseases such as glaucoma that require daily self-administration of eye drops effective therapy can be limited by poor patient compliance.

Ozurdex, although this is not an issue for Durasert. More important, neither system is well suited for the delivery of biologics, such as proteins and antibodies. Treatment of retinal disease with biologics such as Eylea®, Lucentis® and Avastin® and delivery of biologics to the back of the eye is increasingly important in ophthalmology.

pSivida's Tethadur, a new platform technology, is designed to provide long-term sustained ophthalmic delivery of biologics. Tethadur is a suspension of micronised particles of oxidised meso-porous silicon with a therapeutic drug or biologic, which is injected into the eye. The material slowly dissolves to form silicic acid and is thus slightly acidic, providing an electrostatic attraction with proteins such as Eylea and Lucentis (which have an isoelectric point of over 8). As the material dissolves, the drug or biologic is absorbed into the eye on a sustained basis.

The surface area of Tethadur is extremely large (>200 m^2/g) so the material has a high binding capacity (typically over 10% wt/wt). Further, the diameter of the pores of Tethadur can be manufactured to sizes ranging from 2 to 30 nm to accommodate differently sized therapeutics. Loading the therapeutics into the pores prevents them from aggregating prior to delivery. Furthermore, the attraction between the therapeutic and the pore is a function of the proximity of the pore walls to the therapeutic. This allows the size of the pores to control the release rate. The tighter the fit, the more slowly the therapeutic is released. Using this technology, pSivida has developed systems designed to provide sustained delivery of biologics and drugs for months.

In ophthalmology, there are many potential applications for longer-term sustained release. In traditionally well-managed diseases such as glaucoma that require daily self-administration of eye drops (Figure 2), effective therapy can be limited by poor patient compliance. In more recently treatable disease such as wet AMD, current therapy necessitates regular, as frequently as monthly, injections into the eye. These injections have potential risks such as infection and also present patient compliance issues, but the alternative currently is rapid loss of vision. A sustained-release system for the biologics that treat wet AMD and other retinal diseases should be a significant advance for patients and physicians alike.

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For some presently untreatable diseases, such as dry AMD, which results in a slow loss of vision, the slow progression of the disease makes sustained-release treatment even more desirable.

New therapies are expected to transform treatment of retinal disease in the coming years. Effective sustained release delivery will be key to the success and efficacy of these therapies.