



Sun Pharma – Seciera Potential in Dry Eye Market

Seciera Positioning
Restasis Genericismation Impact
Threat from Pipeline Drug Candidates

Seciera / OTX-101 Potential In Dry Market – Our View



- Dry eye is primarily an inflammatory disease. Restasis and Xiidra are the only treatment options on the market that target inflammation
- Seciera if approved would directly compete with Restasis and Xiidra
- Clearly Seciera has to be the preferred choice over Restasis because of:
 - ✦ **Faster onset of action**
 - ✦ **Superior tolerability**
 - ✦ **Demonstrated statistical significance in improving clinical signs (corneal staining, Schirmer test, conjunctival staining).**
- Like Seciera, Xiidra too has a faster onset of action, but the evidence on improvement in clinical signs (corneal inflammation and improvement in tear production) is mixed. Seciera has the potential to differentiate on these grounds
- Market research shows 70% of patients who were prescribed Restasis dropping out of the treatment within a year for lack of efficacy/tolerability reasons.
- Impact of Restasis genericisation will be limited as there is a large dry eye patient pool awaiting treatment options that can offer better efficacy. Besides, Restasis being a complex drug to copy, we expect limited competition and hence limited price erosion.
- Less than 0.5mn out of 4.5mn patients who have severe dry eye condition (eligible for anti-inflammatory therapy) are currently receiving prescription drugs to address the underlying inflammatory condition.
- Quite a few exciting dry eye drug candidates are under development, but these are 3-4 years away from launch.
- We expect Seciera to be US\$400mn to US\$600mn peak sales opportunity for Sun Pharmaceutical Industries (Sun Pharma).

About Seciera / OTX-101 and Dry Eye Market



- Sun Pharma's NDA filing on Seciera (nanomicellar Cyclosporine A) for the treatment of dry eye was accepted for review by the USFDA in December 2017. A favourable review will potentially mean a launch in calendar year 2018.
- Dry eye is a condition in which there are insufficient tears to lubricate and nourish the eye. Tears are necessary for maintaining the health of the front surface of the eye and for providing clear vision. When severe and left untreated, this condition can lead to pain, ulcers or scars on the part of the eye called the cornea which translates to tearing, redness, pain, soreness, and blurred vision.
- **About 22% of the patients visiting ophthalmologists are dry eye patients.**
- Seciera or OTX-101 is a novel formulation of widely used drug Restasis (Cyclosporine) for dry eye treatment.
- Currently dry eye disease is primarily treated with artificial tears (OTC drugs), while only a small fraction of patients are treated with prescription drugs.
- Restasis (Cyclosporine, US\$1.6bn) was the only prescription drug approved for dry eye since long, until the recent approval for Xiidra (Lifitegrast, US\$200mn). Seciera, if approved, will be the third drug in the market. OTC drugs, which include lubricants / artificial tears, garner around US\$540mn in sales annually.
- There are 20mn-30mn dry eye patients in the US, of which only 0.4mn are treated with prescription drugs. Prescription drugs have not seen penetration for two reasons:
 - Higher cost – Prescription drugs are almost 20x-30x expensive than OTC lubricants.
 - Reimbursement – Insurance plans require patients to fail on multiple trials of OTC lubricants before they can be prescribed prescription drugs.
 - Efficacy is limited and most patients fail to get a satisfactory response.

About Seciera / OTX-101 and Dry Eye Market

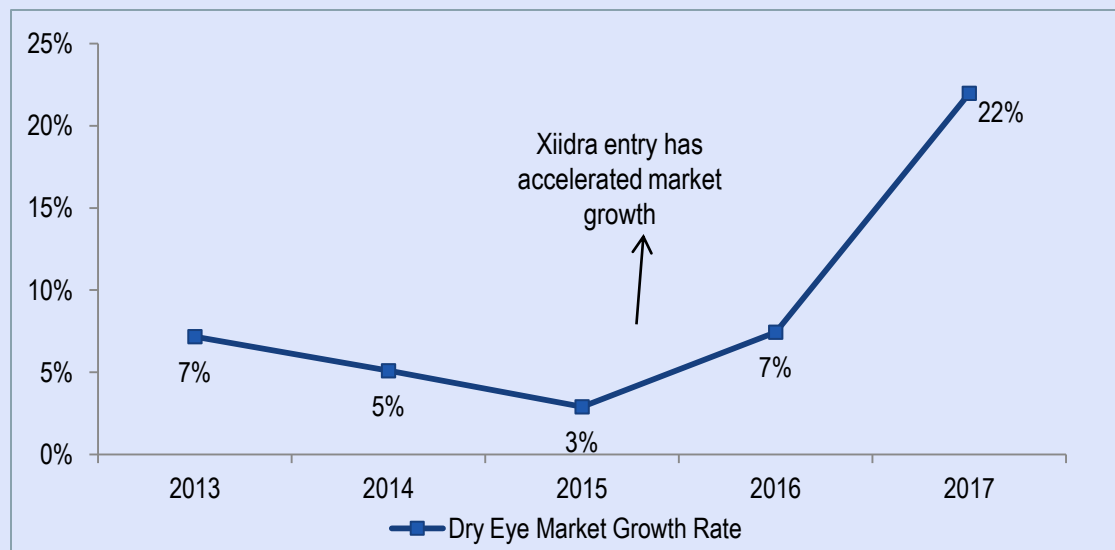


- Seciera is a nanomicellar formulation of Cyclosporine A in a preservative free aqueous base. Restasis comes as an oil-in-water emulsion which leads to typical tolerability issues (burning of the eye).
- Seciera is expected to offer the following benefits:
 - Enhance ocular bioavailability of Cyclosporine.
 - Improve tolerability as nanomicellar formulation allows it to be delivered in a preservative free aqueous solution.
 - Seciera has higher concentration (0.09% vs. 0.05%) of Cyclosporine and hence has the potential to be more effective.
- In Phase 2/3 studies, Seciera demonstrated statistically significant improvement in key endpoints:
 - **Tear production** – As measured by Schirmer test
 - **Reduction in eye inflammation** as measured by corneal and conjunctival staining score.
 - Reported 30% improvement in **SANDE score** (to measure symptomatic improvement) which was comparable to vehicle.

Dry Eye Market In the US – Impact of Xiidra Entry



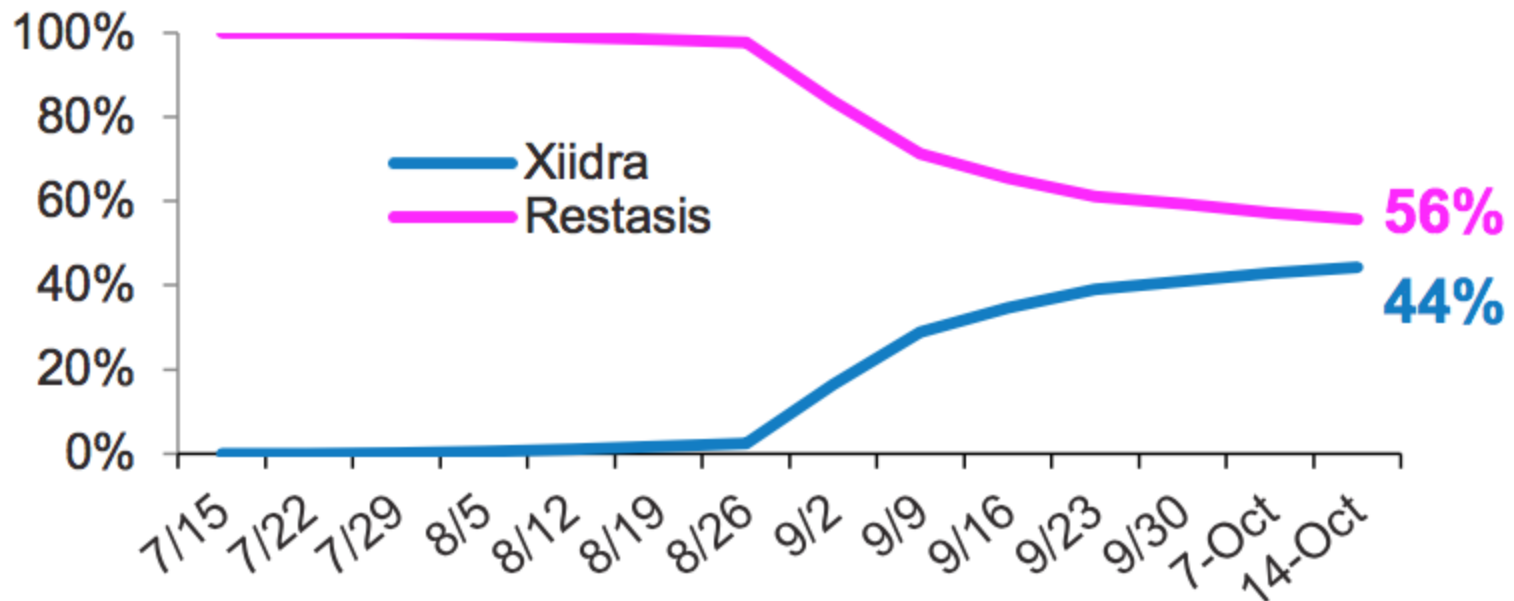
- Prescription dry eye market is worth US\$1.8bn in annual sales, primarily dominated by Restasis.
- Xiidra, which was recently approved, led to an expansion of this space with the market growing 22% YoY in volume terms in 2017.
- The acceleration in growth rate points to the fact that physicians are using Xiidra in patients who do not attain satisfactory response to Restasis treatment . This hints at a latent patient pool that is awaiting for superior /novel treatment options.



Xiidra Versus Restasis – NBRx Share



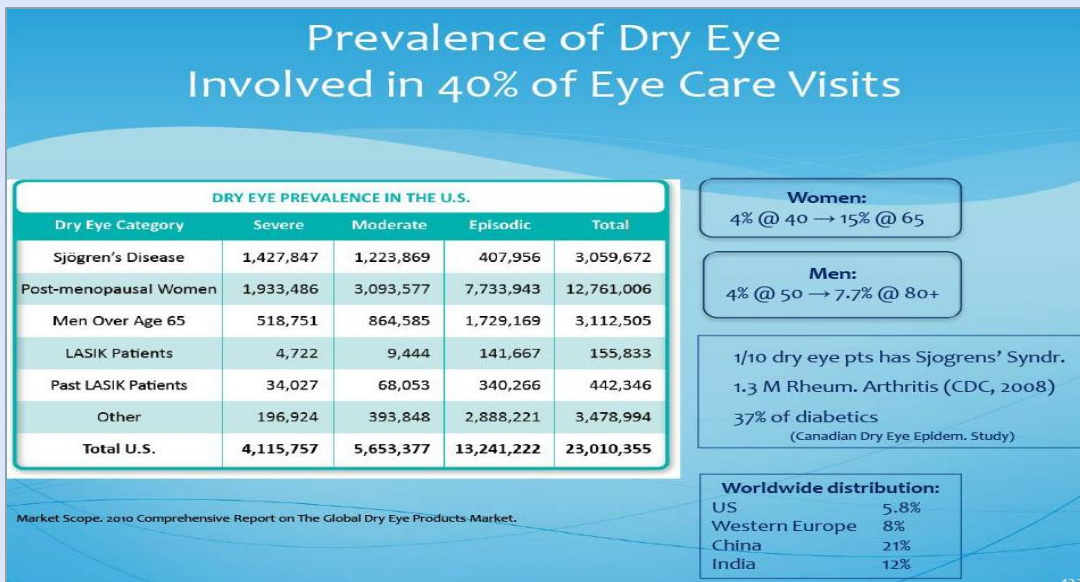
44% XIIDRA New-to-Brand Market Share



Untapped Dry Eye Market Opportunity



- It is estimated that about 20m to 30mn patients in the US have dry eye syndrome.
- About 4.1mn patients have a severe manifestation of Dry Eye
- At the current market size (\$1.8bn) the estimated number of patients on prescription treatment is estimated at about 0.4mn, which implies there is potential for the market to expand multifold.
- The market is largely underpenetrated as there are limited treatment options, limited efficacy, reimbursement hurdles and not all patients respond satisfactorily.



Source: Aurinia Pharma

Table 1. Classification of Dry Eye

Type of Dry Eye	Schirmer test	TBUT
Mild	10 to 15mm	8 – 10 secs
Moderate	5 to 10mm	5 -8 secs
Severe	<5mm	<5 secs

Source: www.medicaljournal.in

Is Seceira Differentiated To Expand The Market?



- Currently, USFDA-approved prescription treatment options for dry eye include Xiidra (Lifitegrast) and Restasis (Cyclosporine).
- **Tolerability** - Based on Phase-2/3 evidence, the key aspect of differentiation is that Seciera is associated with a lower rate of burning sensation on instillation versus Restasis.
- **Symptomatic improvement** - In terms of onset of action, Seceira provides relief from the 12th week onwards, in line with Xiidra, but Restasis take as long as six months.
- **Clinical improvement** – Seciera has demonstrated evidence in terms of improvement across all clinical endpoints -corneal staining, conjunctival staining and Schirmer test. The evidence on Restasis and Xiidra so far has been inconsistent.

Seciera can be the new Gold Standard



- **Statistically significant superiority across clinical endpoints** – In Phase-2/3 clinical trials, Seciera has demonstrated superiority across endpoints like:
 - **Conjunctival staining** – Used to detect early signs of damage due to dry eyes – **Seciera has demonstrated statistically significant improvement in the conjunctival staining** score compared to placebo, while Restasis and Xiidra have not shown statistically significant reduction comparable to placebo.
 - **Corneal staining** - a measure of eye damage in the corneal regions - In case of Xiidra, study results were inconsistent as they demonstrated statistically significant reduction in only one out of three Phase -3 studies. Same was the case with Restasis. **Seciera has demonstrated statistically significant reduction in the corneal staining score.**
 - **Schirmer test measures tear production** –
 - ✦ In case of Seciera, tear production was superior with both concentrations of the active treatment compared with the vehicle. The 0.09% drug concentration was significantly ($p = 0.007$) better compared with the vehicle and resulted in 17.9% of the patients having a 10mm or greater improvement in Schirmer test compared with 7.6% of patients assigned to the vehicle.
 - ✦ Xiidra did not demonstrate statistically significant improvement over the vehicle across all studies.
 - ✦ Restasis results are comparable to Seciera on the Schirmer test endpoint. 15% patients on Restasis achieved 10mm or greater improvement on Schirmer testing as compared to 5% on placebo.

Seciera can be the new Gold Standard



- **Superior performance in reducing central corneal inflammation - a more relevant endpoint -**
Unlike Restasis and Xiidra, Seciera has shown benefit in central corneal inflammation which has higher correlation with dry eye symptoms.
The central cornea has five to six times as many nerve fibres as the peripheral cornea. Consequently, corneal sensitivity is higher in central cornea compared to the periphery. It may be noted that symptoms of dry eye are more prevalent in patients who exhibit greater ocular surface damage of central cornea.
- **Lower burning sensation -** The most commonly reported adverse effect with OTX-101 and Restasis is burning upon instillation of the drops, which can affect patient compliance. With Restasis, about 17% of the patients reported burning on instillation. In contrast, 1.3% of patients assigned to both OTX-101 concentrations reported severe discomfort. Moderate or severe instillation site pain or discomfort was reported by only 5.6% of the patients receiving active treatment.
- **Early onset of action –** Seciera improves tear production in patients as early as 12 weeks, (in line with Xiidra), but much quicker than Restasis which takes as long as six months.

Limitations Of Cross -trial Comparison In Dry Eye Disease

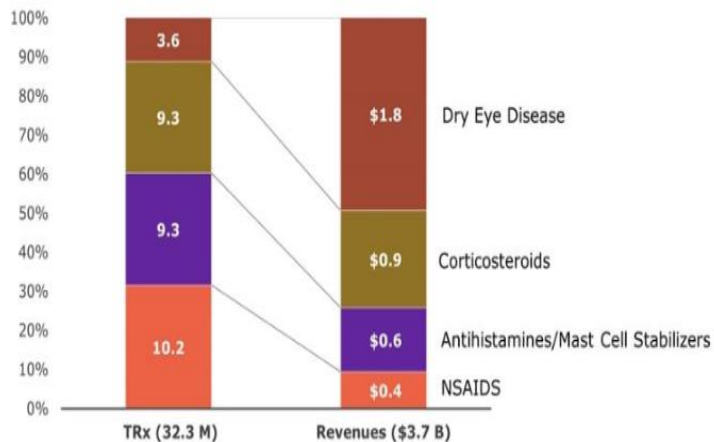


- Cross-trial comparisons in dry eye disease have limited reliability for the following reasons:
 - The disease cannot be objectively measured as the various recommended diagnostic tests lack adequate specificity and sensitivity.
 - Improvement in disease symptoms (dryness, burning, itching) do not correlate with improvement in clinical signs of inflammation (corneal staining, conjunctival staining and Schirmer test).
 - The diagnostic test for symptom improvement in clinical trials are not comparable.

Impact of Restasis Genericisation on Seciera Market Potential



US Eye Drop Market in 2016



Source : Aldeyra Therapeutics

Taking a clue from genericised opportunities within the ophthalmic space, we forecast Seciera sales in dry eye market under various scenarios (**price erosion, volume growth and market share**):

Scenario - 1- US\$450mn

Scenario - 2- US\$500mn

Scenario - 3- US\$550mn

The key assumptions being:

- 1) **Pricing of Seciera post Restasis genericisation – Expect limited price erosion post genericisation as Restasis is a complex generic.**
 - 1) **Scenario - 1**— Remains at current level of US\$5,000 per annum
 - 2) **Scenario - 2**—30% discount to current prices
 - 3) **Scenario - 3**— 50% discount to current prices
- 2) **Prescription volume growth over five years in dry eye market –The hypothesis being that penetration will improve in patients with severe dry eye which is currently just at 10%.**
 - 1) **Scenario - 1**— 1.7x of current volume (penetration at 17%)
 - 2) **Scenario - 2**—2.0x of current volume (penetration at 20%)
 - 3) **Scenario - 3**— 2.5x of current volume (penetration at 25%)
- 3) **Seciera market share based on cross-trial comparison.**
 - 1) **Scenario - 1**— 15%
 - 2) **Scenario - 2**— 20%
 - 3) **Scenario - 3**— 25%

Drugs in the Pipeline for Dry Eye Disease



- The dry eye drug pipeline can be categorised into two parts:
 - Novel Cyclosporine formulations
 - Novel molecules

Novel Cyclosporine Formulations in Phase 3 development



- **CyclaSol – Phase 2/3 – Novaliq**

Currently, in Phase-2/3 and being developed by Novaliq. Head to-head Phase 2 studies suggest superiority over Restasis. Approval can be expected in FY21/FY22. Unlike Sun Pharma, which has not compared its formulation with Restasis in head-to-head trials, CyclaSol will come with a superiority label if it is able to replicate Phase-2 success in Phase-3 trials.

- **Voclosporin – Phase 1 – Aurinia Pharmaceuticals**

Voclosporin has a mechanism of action similar to Cyclosporine (calcineurin inhibitor). Phase-2 trials will commence shortly and are expected to be completed by the end of CY18. Approval can be expected in 2022. Unlike Sun Pharma's Seciera, Aurinia too is conducting a head-to-head trial against Restasis, which showcases the company's confidence in the product. Phase -1 safety and tolerability studies have concluded, which indicate that Voclosporin has a faster onset of action and has demonstrated improvement in dry eye symptoms and also tear production.

Novel Molecules For Dry Eye Treatment



- **SYL-1001 (Phase 3, Sylentis, TRPVI inhibitors)** – Phase-3 trials have begun and are expected to be completed in December 2018. If Phase -3 trials are successful, approval can be expected in 2020. Phase-2 trial data has shown limited benefit. In Phase-2 studies, statistically significant improvement was seen in symptoms - ocular pain and conjunctival hyperemia, but SYL-1001 failed to show statistically significant improvement in clinical signs which include corneal staining, tear break-up time and Schirmer test.
- **ECF843 (Phase -3, Lubricin / Alcon, Recombinant Natural Peptide)** – Novartis/Alcon have in-licensed rights from Lubric LLC to develop and commercialize Lubricin outside Europe. Lubricin is recombinant of naturally occurring protein in the eye that is responsible for lubricating the eye and preventing evaporative loss of tears. In Phase 2 trials, Lubricin met the primary endpoint. Patients that received Lubricin supplementation achieved greater than 72% reduction from baseline in foreign body sensation ($P < .013$), burning/stinging, pain, sticky feeling ($P < .0432$), blurred vision ($P < .0013$), and photophobia ($P < .011$) in at least one eye. Lubricin also showed significant improvement in fluorescein staining (OD/OS: 43.8%/50.0%, vs. 26.5%/23.3%, $P < .0398$, $P < .0232$), TFBUT ($P < .010$), SANDE frequency ($P < .0435$), eyelid erythema ($P < .004$), conjunctival erythema ($P < .0013$), and instillations ($P < .04$) as compared to HA. Alcon is yet to initiate Phase-3 trials on Lubricin. We expect Lubricin to be commercially launched in 2021.
- **ADX-102 (Phase-3, Aldeyra Therapeutics, Aldehyde Trap)** – Pivotal Phase -3 trials are likely to be initiated in 2019. The company reported Phase-2 trials outcome recently. Phase-2 trials did not have a placebo arm and hence results of cross-trial comparison may not be fair in this case. But the company has shown statistically significant reduction over the baseline score on both symptomatic and clinical sign endpoints. The company will shortly begin Phase-2b trials, wherein it will compare ADX-102 to a vehicle arm.

Novel Molecules For Dry Eye Treatment



- **Tavilermide (Phase -3, Allergan/Mimetogen, Neutrophin Mimetic)**– Allergan has in-licensed rights for Tavilermide from innovator Mimetogen. Phase -3 trials on Tavilermide has been recently completed and the data is yet to be reported. Tavilermide is a neurotrophin mimetic that acts as a partial agonist of the nerve growth factor receptor TrkA.
In Phase-2 trials which evaluated symptomatic and improvement in clinical signs post four weeks of treatment, the evidence pointed to a positive effect but statistical significance was not achieved. Tavilermide did not demonstrate statistical significance over placebo, but there was evidence of positive effect.
- **RGN-259 (Phase -3, RegenerX, Thymosin Beta 4)**- RGN-259 is an antagonist of Thymosin Beta-4, a peptide naturally found in various human blood cells that has anti-inflammatory activity and promotes tissue repair. RGN-259 demonstrated a rapid onset of action in a Phase-2 clinical trial and is being developed in a preservative-free formulation. On the final day of dosing (Day 28), patients receiving 0.1% RGN-259 had a statistically significant reduction in ocular discomfort during CAESM (Controlled Adverse Environment) exposure when compared to placebo (Intent-to-Treat Population (ITT), $p=0.043$). Importantly, this result was also observed in previous Phase-2 trial in patients treated with 0.1% RGN-259 (ITT, $p=0.024$), thereby demonstrating a symptom endpoint in two independent trials. A statistically significant ocular discomfort improvement after CAESM exposure on Day 28 was also observed in the 0.05% and 0.1% RGN-259 treatment arms when compared to placebo (ITT, $p=0.0366$ and $p=0.0072$, respectively) indicating a dose- dependent response.
- In this population, patients receiving 0.1% RGN-259 had a statistically significant reduction in corneal fluorescein staining prior to entering the CAESM on Day 28 when compared to placebo ($p=0.034$). The same result was observed in previous Phase-2 trial for patients treated with 0.1% RGN-259, although it was not statistically significant in the smaller sample size of this previous Phase-2 trial. Additionally, a change from baseline analysis (Day 28 minus Day 0) demonstrated statistically significant improvement in inferior corneal staining for the 0.1% RGN-259 treatment arm when compared to placebo ($p=0.003$). This finding was also observed at Day 14 compared to placebo ($p=0.035$). The data suggests that RGN-259 has a fast-acting treatment effect on dry eye sign after 14 and 28 days of dosing.

View – Seciera Positioning In Dry Eye Market



- Current dry eye treatment options offer limited satisfaction as only a fraction of patients are able to reach the treatment goal. As dry eye is a multifactorial disease, a variety of approaches including combination treatment is required. Newer treatment options as they reach the market will expand the market.
- Currently less than 0.5mn out of 4.1mn severe dry eye patients are being treated for inflammation.
- Seciera is differentiated to the extent that it has a superior onset of action which is critical, as in the absence of symptomatic improvement patients tend to discontinue treatment because they perceive it to be ineffective.
- Clinical evidence suggests that Seciera addresses inflammatory aspect more efficiently than Restasis. This is probably because of better ocular bioavailability (nanomicellar formulation) and a higher dose concentration (0.09% vs. 0.05%).
- Tolerability issues like burning on instillation are much lower with Seciera than Restasis as Seciera comes in an aqueous solution, while Restasis comes in an oil-in-water emulsion.
- Pipeline candidates under development are about 3-4 years away from the market. A few which have demonstrated strong evidence in early stage trials include Lubricin, Voclosporin, CycloSol and RGN-259. We believe once the newer treatment options are introduced, these shall expand the market. This is also evident from the fact that Xiidra entry into the dry eye space has led to the market growing @ 22% as against the traditional growth of mid to high single-digit.



ANNEXURE

How Is Dry Eye Diagnosed



Practical Sequence of Dry eye Tests

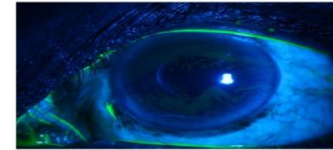
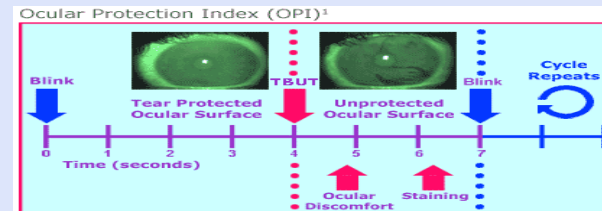
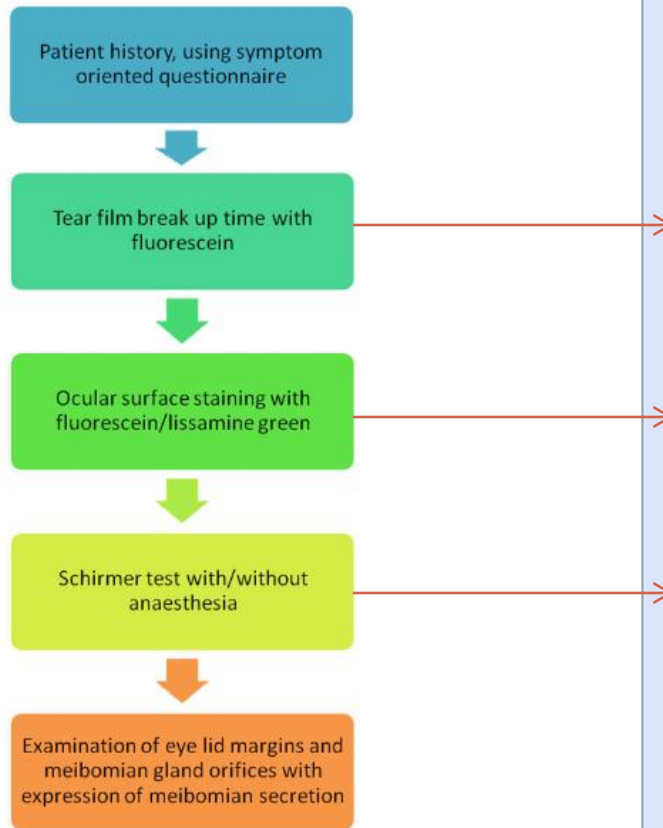


Figure 5- Fluorescein Dye staining of cornea and Conjunctiva in mild to moderate Dry eye disease



Figure 4
Schirmer's Test to assess Tear film. Results less than 10 mm without anaesthesia considered abnormal. Consistently low Schirmer test readings are suggestive of aqueous tear deficiency

Why Dry Eye Needs to be Treated



- Dry eye is a chronic progressive disease.
- Dry eye can make it more difficult to perform some activities such as using a computer or reading for an extended period of time, and it can decrease tolerance for dry environment such as the air inside an airplane.
- In the long term, if left untreated, the corneal surface is damaged, making eyes more prone to infection and in rare cases vision is also impacted.

Dry Eye Treatment Goals



- Improvement in disease symptoms (pain, irritation, foreign particle sensation, blurred eye).
- Improvement - clinical signs:
 - Restoring corneal surface and preventing progressive damage – This is measured by corneal staining score.
 - Restoring conjunctival surface and preventing progressive damage – This is assessed by conjunctival staining score.
 - Restoring tear production – Measured by Schirmer test and TBUT - (Tear Break-up Time).

Existing Treatments Have Limitations



- It takes long for patients to notice a change in the condition with Restasis.
- A survey of ophthalmologists suggests a significant proportion (20%-80%) of patients failing the treatment (artificial tear drops and Restasis).
- Artificial tears improve clinical signs, but these need to be frequently dosed and do not address inflammation which is crucial to prevent progressive damage to tear-producing glands.
- Burning sensation on instillation is a common side effect with Restasis reported in 17% of the patients.

Restasis Versus Xiidra



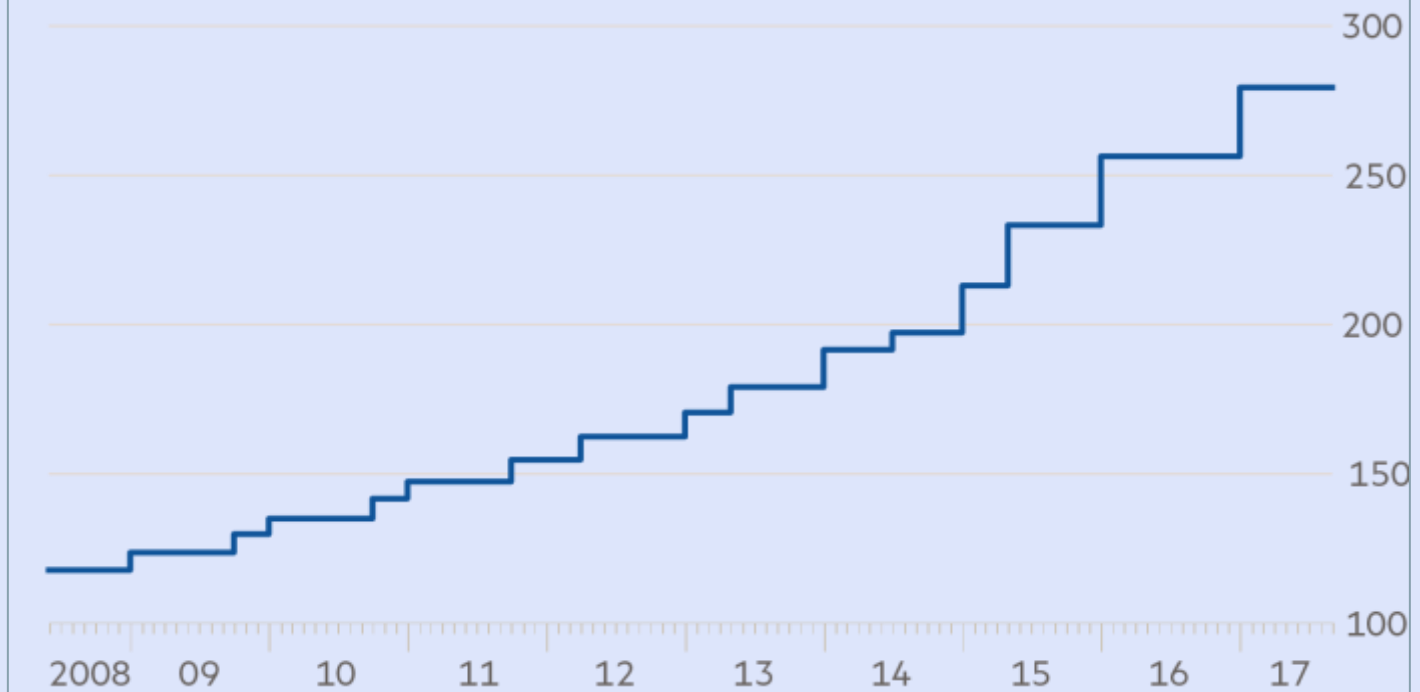
- Both Restasis and Xiidra treat underlying inflammation, but they vary from each other in terms of
 - Onset of action – Xiidra can improve tear production in just 12 weeks, while it takes 6 months for Restasis to provide similar improvement
 - Scope of improvement in Clinical Signs – When it comes to improvement in clinical signs, both Restasis and Xiidra have produced limited success as they failed to consistently prove a statistically significant improvement in corneal staining score / conjunctival staining score across all trials
 - Safety and Tolerability – Xiidra is associated with bad taste, while Restasis is associated with a burning sensation.
- Unlike Restasis, Xiidra has a wider label. Restasis label is restricted to improvement in tear production in dry eye patients, while Xiidra label also includes improvement in symptoms (itching, redness, blurred vision, foreign body sensation)
- Xiidra is associated with dysgeusia (bad taste) which affects patients tolerability.

Restasis Price



The price of Restasis has more than doubled since 2008

Average wholesale price for a 30-dose pack (\$)



Source: FT Research

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