

CLINITAS ULTRA 3

TECHNICAL PRODUCT SUMMARY AND CLINICAL DATA

The Product

Clinitas Ultra 3 was designed following careful study of the tear film in the normal eye and in disease states. According to the “Unified Tear Film Theorem”,¹ the tear film must exist at all times, continuously under the lids and between the lids. To achieve this, treatment for tear film abnormalities needs to be able to wet the hydrophobic ocular surface to form a smooth surface that remains intact for the duration of a blink. Different commercial artificial tear preparations have concentrated on similar strategies to achieve this; most of these are based on the use of increased viscosity to increase retention time. The approach adopted for Clinitas Ultra 3 is unique in several ways.

Clinitas Ultra 3 is an innovative, optimised sterile eye drop which is formulated with components with physical properties which individually mimic each of the three layers of the tear film. This provides a holistic approach to protect from predominantly evaporative conditions. There are three key components of the product:

- blended polymers,
- proprietary phospholipid mixture and
- a soft preservative.

Mechanism of Action

¹ Holly FJ. 2005 “What to do when you have dry eye.” Presented at 8th Triennial Meeting of the International Society of Dacryology and Dry Eye. Madrid April 2005.

Clinitas Ultra 3 uniquely protects the corneal surface by delaying tear evaporation through restoration of the lipid layer of the tears, boosting the aqueous component and enhancing the wettability of the ocular surface by stabilising the mucin layer.

- The polymer mixture consists of two forms of polyvinyl alcohol (87% Hydrolysed, 0.9%, 99% Hydrolysed, 1.8%) and povidone 2%. Polyvinyl alcohol combinations are known to increase the persistence of the tear film and, when combined with povidone, have mucoadhesive action making them a better choice when the ocular mucin surface is reduced.² In Clinitas Ultra 3, the polymers are synergistically blended together to have a colloid osmotic pressure of 65mmHg compared to 4mmHg in other formulations. When epithelial breaks occur, the ocular surface is no longer impervious to water. Due to its high colloid osmotic pressure, Clinitas Ultra 3 is capable of removing excess intercellular fluid. This in turn facilitates resolution of epithelial breaks.
- The phospholipid containing component is the proprietary, patented Amisol[®] Clear, which contains phospholipid (lecithin), polysorbate-80, and glycerine. Amisol Clear is well tolerated having excellent Draize testing results. The role of Amisol Clear in Clinitas Ultra 3 is multiple:
 - o the phospholipids are responsible for stabilising the lipid layer;
 - o reducing evaporation from the ocular surface;
 - o It is also a dispersing agent and prevents the formation of polymeric aggregates, which could form due to the high concentration of polymers in this formulation. It also prevents crystallisation of polymers on eyelashes.
- The product is preserved with polyquaternium 42 an effective antimicrobial and antifungal agent with low corneal irritation which also has the benefit of surfactant properties to increase the surface wetting.

² Simón-Castellví GL, Simón-Castellví S, Simón-Castellví JM, Simón-Castellví CS, Simón-tor JM, Pita-Salorio D. Tear Supplements – Artificial Tears. In Dry Eye: a practical guide to ocular surface disorders and stem cell surgery. Agarwal A (ed.) Publ. Slack Inc. 2006. Chapter 11.

- The product is buffered to maintain pH in the mid range so that it is very slightly acidic (specification range is 6.5 to 6.9). The viscosity of the product is relatively low compared to some other artificial tear preparation making prolonged blurred vision after instillation much less likely. As explained above, Clinitas Ultra 3 does not depend on its viscosity for a prolonged effect.

Clinical Studies and Information

1. Study No APL01

Investigator Centre Dr W Trattler, Cornea and External Diseases, Miami, Florida US

Design An open evaluation of 10 eyes from 5 patients previously treated with alternative artificial eye drops using a questionnaire and clinical examination.

Methodology Each subject had three visits in the study. At each visit, subjects underwent a study assessment which comprised a clinical examination (corneal surface and Tear Break Up Time) and completion of a dry eye questionnaire. The questionnaire asked subjects to rate burning, grittiness and tired and dryness on the following scale:

1=My Eyes do not feel this way at all

2=My eyes feel a little this way

3=I have this symptom a substantial amount of time

4=I notice these symptoms all the time and it does interfere with my normal activities

Each subject used Clinitas Ultra 3 between the first and third visits.

Results

1. Subject Rating of dry eye sensations

The following table summarises the results obtained

Table 1 Mean subject questionnaire rating for each parameter (n=5)

Parameter	Pre Clinitas Ultra 3 (Visit 1)	Post Clinitas Ultra 3 (Visit 3)
Burning	2.2	1.0
Grittiness	2.6	1.25
Tired and Dry	3.0	1.25

After using Clinitas Ultra 3, patients reported an improvement in the severity of burning sensation (55%), gritty sensation (52%), feeling of tiredness or dryness (80%).

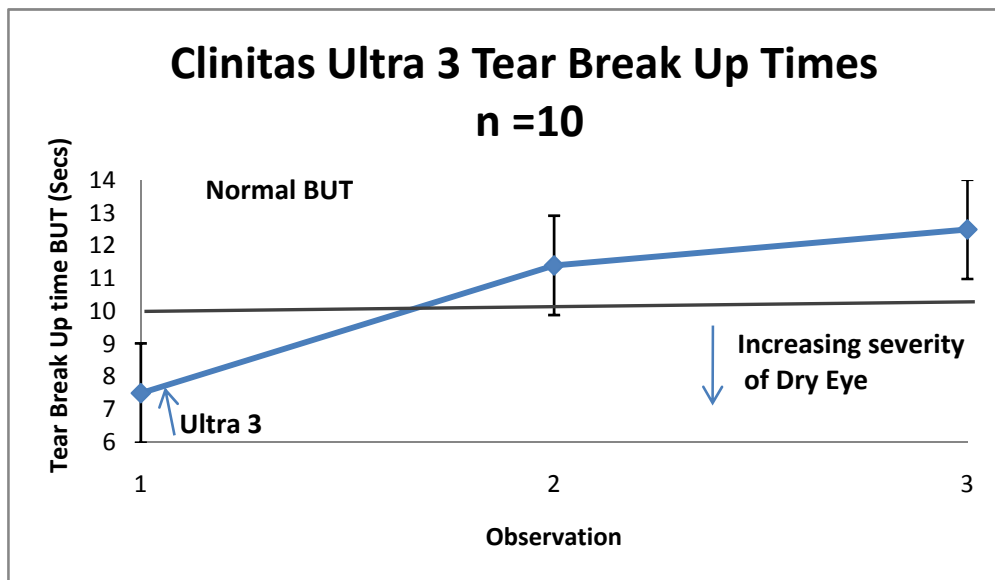
2. Ocular Surface and TBUT

a Ocular surface, on clinical examination the Investigator noted improvement in the ocular surface in all patients.

b. Tear Break Up Time

All patients showed an improvement in Tear Breakup Time (BUT).³ The following Figure 1 shows the data obtained when patients were observed after one and two weeks of Clinitas Ultra 3 treatment.

Figure 1 Tear Break Up Times after Clinitas Ultra 3



In these subjects with dry eye, break up time before treatment was 7.5secs \pm 2.0. Values for TBUT of less than 10 seconds are regarded as indicative of dry eye confirming that all subjects

³ Trattler B. 2002. APL-105 Clinical Study Tear Breakup Time, Patient Questionnaire Results & General Observations. Data on file.

were appropriate for inclusion. After administration of Clinitas Ultra 3, there was a 66% improvement in TBUT.

Conclusion

The Investigator concluded 'that in his patients with significant dry eye problems related to poor tear film quality had significant improvements both subjectively and objectively.'

2. Study 2 APL02

Investigator Centre Dr D W Lamberts, Lubbock, Texas, US

Design A crossover comparison of APL 105 (Clinitas Ultra 3) and Tears Naturale in 11 patients with moderate/severe Keratoconjunctivitis Sicca (KCS) or Sjogren's syndrome

Methodology Subjects were enrolled into the 4 week study after clinical confirmation of KCS or Sjogren's syndrome. Throughout the study patients administered both control and test drops, one preparation to the left and the other to the right eye. After 2 weeks, the treatments were crossed over so that the test and control were administered to the contralateral eye. There were 3 visits and at each occasion the following assessments were made:

Clinical Signs

1. Degree of vital staining by Lissamine Green, scale 0 to 9
2. Width of tear meniscus, mm
3. Degree of redness, scale 0 to 4
4. Degree of mucus precipitation in the eye, scale 0 to 4

Subjective Symptoms

1. Degree of burning, scale 0 to 4
2. Degree of dryness, scale 0 to 4
3. Degree of blurred vision, scale 0 to 4
4. Degree of foreign body sensation, scale 0 to 4

Summary Results

Eight patients completed the study and the other 3 partially completed. Thus in total the test and control drops were each tested on 19 eyes. The ranking of the parameters assessed showed that in 7 out of 8 metrics, Clinitas Ultra 3 was superior to Tears Naturale. There was no difference for tear meniscus measurements. More importantly, 90% of the eyes showed better healing of the corneal staining with the test solution and none showed better healing with the control.

Conclusion

Tears Naturale contain hypromellose and dextran. The results have shown, in this severe group of patients that can be expected to have a lipid deficiency that Clinitas Ultra 3 performs better than the comparator product, being longer lasting and more effective on the various parameters measured.

3. Other Studies

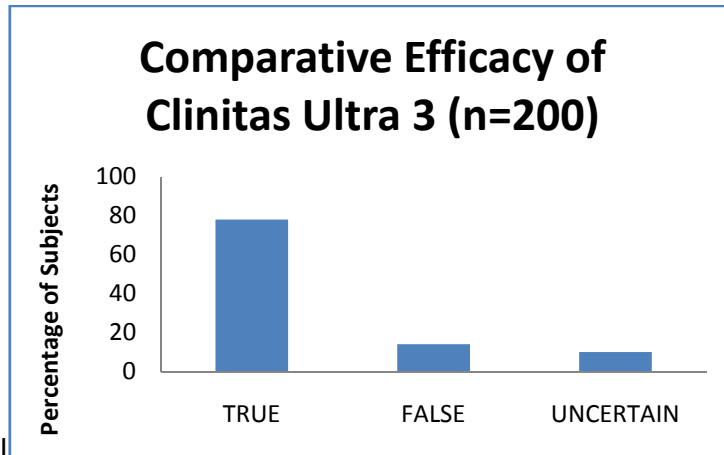
Two further studies have been performed.

Mason evaluated Clinitas Ultra 3 in 11 patients. All the 9 patients that completed reported improved comfort, and reduced need to lubricate than with their prior drops or gel. One patient, a moderate KCS sufferer went from drops every ½ to 1 hour to 2 -3 drops daily. All 9 patients also showed reduced corneal staining with fluorescein and Lissamine Green; 3 patients had total regeneration of the corneal epithelium. Tear breakup time (invasive and non-invasive technique) was unchanged in 4 patients and improved in 5 patients after a 2-week treatment period. 2 patients discontinued the use of the product due to discomfort and stinging judged by Dr Mason to be due to severe corneal damage present prior to commencement of the study.⁴

Clinitas Ultra 3 was also evaluated in an open survey involving more than 200 patients. Participants were asked whether the use of Clinitas Ultra 3 helped their condition more than other regimes that they had tried. Seventy-six (76%) of patients gave a positive feedback (Figure 2)⁵ These data were presented at the Tear Film and Ocular Surface Society (TFOS) meeting in Puerto Rico 2004.

⁴ Mason G. 2002. Letter to Dr F Holly and Mr J Echols. Data on file.

⁵ Holly FJ. 2004 Open Clinical Trial in Cyber Space on Post-Lasik patients with regard to Dry Eye Management. Presented at the Tear Film & Ocular Society Annual Conference. Puerto Rico Nov. 2004.



Conclusion

Clinitas Ultra 3 is the result of years of research into the tear film in dry eye conditions and normal eyes. The spread of the aqueous component across the ocular surface is facilitated by a purposely selected mixture of polymers. These provide a uniquely high colloid osmotic pressure which removes excess intercellular fluid. The presence of phospholipids stabilises tears and slows their evaporation. Clinical evaluation has found that TBUT is prolonged with benefit to its users.