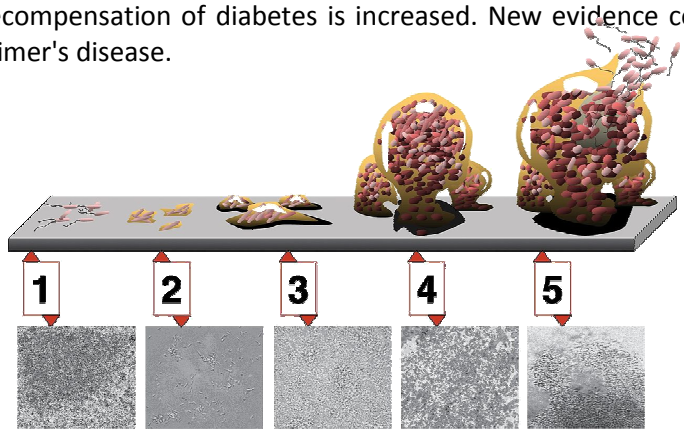
HYBENX®

Oral Tissue Decontaminant

¿QUÉ ES EL BIOFILM?

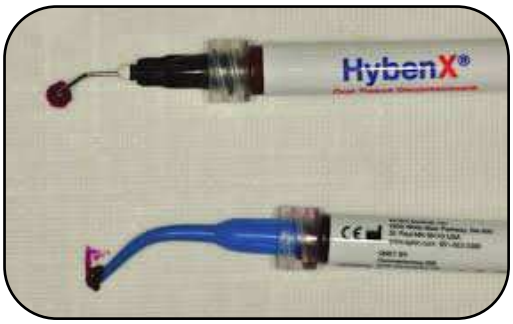
Biofilm is a complex film of microorganisms that live in an organic matrix (formed by polymers and polysaccharides in aqueous phase) strongly attached to the surface of the teeth.
Biofilm formation begins when freely fluctuating microorganisms attach to a surface.
When a group of bacteria accumulate on a surface and reach a particular cell density, a secretion of polymeric substances composed of polysaccharides, proteins and DNA begins, which, associating with free water molecules in the surrounding environment, give rise to a matrix in which bacterial cells are strongly established.
Among these bacteria are pathogens that could not otherwise be accessed and find protection and a suitable breeding ground in the matrix to spread. If these bacteria pass into the blood, the risk of **cardiovascular diseases**, premature births or decompensation of diabetes is increased. New evidence confirms the association between periodontitis and Alzheimer's disease.



HYBENX®
Oral Tissue Decontaminant

¿QUÉ ES HybenX®?

HybenX® is a semi-viscous liquid of violet color for topical use, for local application in the oral cavity.
HybenX® contains sulfonated phenolic compounds and sulfuric acid in aqueous solution.
HybenX® is a Class I medical device, CE certified.

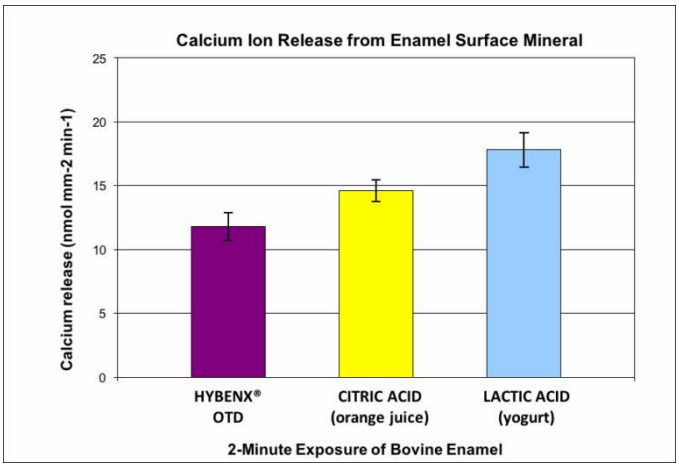


1) **HybenX®** can remove plaque biofilm from hard surfaces (teeth) better than competing products and
2) **HybenX®** has a unique feature in that it also eliminates pain, infection and inflammation in contact with tissues. soft (oral) and on the skin.

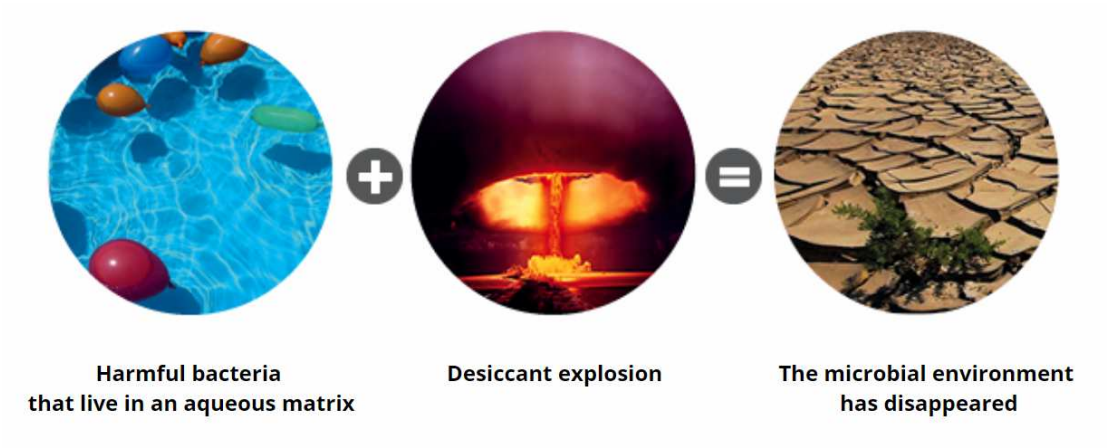
Product adoption is gaining ground for two main reasons:

1) **HybenX®** offer a much lower cost advantage than antibiotics
2) Nothing destroys the biofilm as fast as **HybenX®.** There are other products, such as bleach and phosphoric acid, that are capable of destroying this biofilm on contact; however, these products could never be used as **HybenX®** due to the damage they would do to the soft and healthy mucosa (oral) tissue.

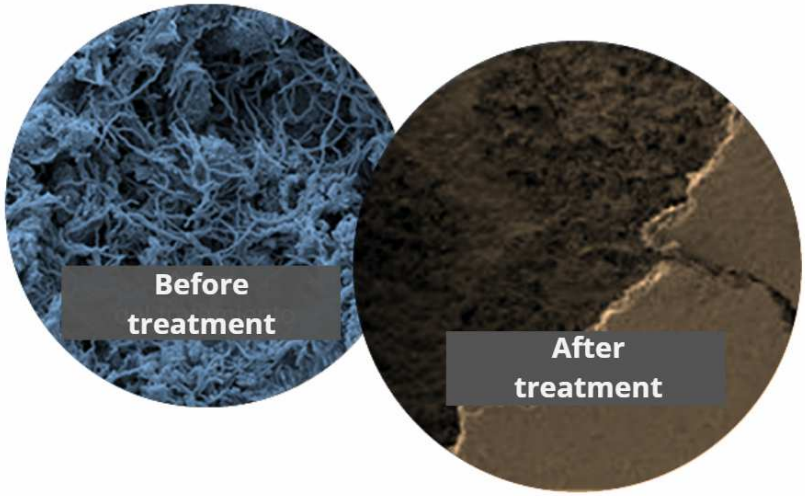
The properties of **HybenX®** are those of a POWERFUL **TISSUE DECONTAMINER.**
Studies have shown that HybenX® causes less erosion on enamel than orange juice or yogurt and does not harm the pulp or periodontium.



HybenX® uses the hygroscopic characteristics of the sulfur present in its composition to quickly and efficiently absorb the water contained in the Biofilm by drying it.

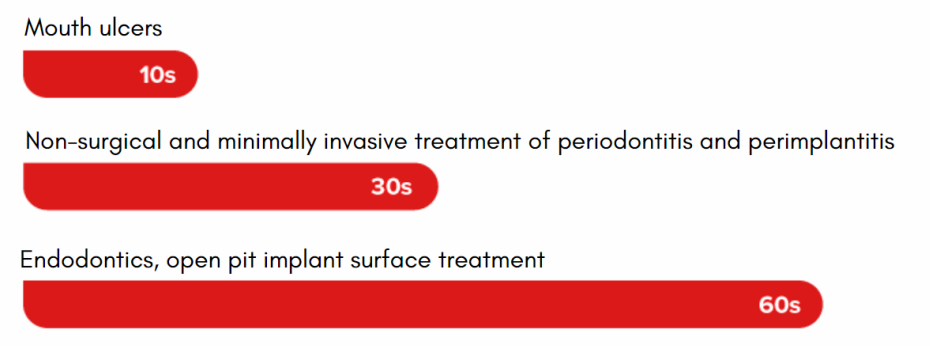


Without the presence of water, the organic polymers that make up the backbone of the Biofilm matrix precipitate.
The entire structure of the Biofilm collapses and separates from the tooth surface and the tissues.
The precipitated Biofilm is easily irrigated and evacuated by surgical aspiration.
Without the presence of water, the organic polymers that make up the backbone of the Biofilm matrix precipitate.



HOW IS IT USED?

As indicated in the instructions for use, the surfaces of the fabrics must always be dried with a cotton gauze and / or compressed air before applying HybenX®.
In cases of excessive bleeding, doctors recommend that the product be applied generously to displace excess blood and fluids. This is because the product is less effective as it is diluted.
The parameters of its application depend on the decision of the Clinician. After the application time has elapsed, wash with physiological solution and vacuum.



WHAT PRODUCT CONFECTIONS ARE THERE?

GEL

2 syringes of 1ml (2ml)

LIQUID

2 syringes of 1ml (2ml)

The use of liquid or gel will depend on whether we have to reach areas of difficult access and where we can control how far the product reaches, in which case we can use the liquid or, conversely, the gel when we want greater control over where we apply the product. and to stay in the area. It is up to the professional to use one presentation or another as well as the application time.

LIQUID

- **Gingivitis**
- **Periodontitis**
- **Post-extraction socket decontamination**
- **Endodontics**
- **Cavities**

GEL

- **Mucositis**
- **Peri implantitis**
- **Impression takings**
- **Osteotomy preparation**
- **Maintenance of prosthetics**
- **Orthodontics**
- **Cold sores**

INDICATIONS:
HybenX is indicated for the removal of plaque biofilm, when, in the opinion of the dental professional, an adjunctive treatment for cleaning is required to remove plaque biofilm. HybenX is a single use product indicated as a
topical rinse/solution that is delivered locally in the oral cavity. HybenX is administered by an irrigation syringe or other means chosen by the dental professional.

DESCRIPTION:
HybenX contains sulphonated phenolics and sulphuric acid, which are tissue denaturants, in an aqueous solution. HybenX is an opaque purple, semi-viscous liquid or gel.

DIRECTIONS:
HybenX is to be used topically only with an irrigation syringe or other means chosen by the dental professional, to the gingival tissues or periodontal pockets surrounding the affected tooth/teeth, dental pulp or the pulpal canal for endodontic treatment. Treatment should start with the deepest portion and to be irrigated thoroughly to the more superficial areas. Excess fluids reduce the effectiveness of HYBENX. Use cotton or compressed air to dry tissues prior to application. For sites with excess bleeding, introduce a generous amount of HYBENX directly at the source of the bleeding to displace the blood. The product should be applied for 10 to 20 seconds. Remove HYBENX by thoroughly irrigating the oral cavity with water and evacuate with high speed suction. Removal of the product is required to stop the cleaning
process. Properly dispose of any remaining product.
NOTE: If the patient has not been given a local anesthetic the product may elicit a stinging sensation during application until it is rinsed off. Incidental contact with any oral tissue will cause it to turn “white“ until the tissue rehydrates itself.
HybenX is contraindicated for use with calcium hydroxide paste and similar, related products. HybenX is intended to be used in its original semi-viscous state. Diluting with water and/or combining HybenX with another product will
render the product ineffective and potentially harmful.
If using HYBENX during Etching procedures, HYBENX should only be applied and removed prior to application of the etching solutions.

IRRIGATION TIP:
Depending on the clinician’s preference, a blunt-locking tip needle or a closedend side-port needle may be used for product application and irrigation. Only the blunt-locking tip is enclosed.

WARNINGS:
Keep out of sight and reach of children. Do not use if the patient is allergic to a material that contains sulphur in any
form.
Because of its nature, prolonged use on normal tissue should be avoided.
HybenX will eventually slough any tissue to which it is applied if excess volume is used and an application time is grossly extended.
It is important to use high speed evacuation/suction to limit overflow of any excess material to areas that do not need to be treated.

PRECAUTIONS:
HybenX is for use in the oral cavity only. Avoid eye contact. If eye exposure occurs, immediately remove any lenses
and irrigate eyes for at least 15 minutes with luke warm water.
If skin contact occurs, immediately rinse thoroughly with water. HybenX will damage clothes or fabric.
Safety and effectiveness in pregnant women and children under the age of 12 has not been established.

ADVERSE REACTIONS:
HybenX may cause local irritation and swelling upon administration. It is important to irrigate liberally with water and evacuate

With the application of HybenX® the clinic immediately obtains:

1) Reduce oral pain and discomfort
2) Remove all disease-causing microorganisms on oral tissue surfaces
3) Detach and destroy dental plaque and plaque bacteria on tooth surfaces
4) Detach and destroy infected, necrotic and dead matter from oral tissue surfaces
5) Eliminate the spread of oral bacteria into the bloodstream during dental procedures
6) Eliminate the spread of oral bacteria into the clinic environment during procedures
7) Stop inflammation and destroy inflammation promoters on oral tissues
8) Stop open bleeding and persistent oozing of blood on diseased oral tissues
9) Reduce oral tissue swelling
10) Seal and protect open ulcerations of oral soft tissue

In other words, HYBENX products can be used by dental practitioners to enhance patient comfort by instantly stopping infectious and inflammatory disease processes while sealing open wounds. They can be used to facilitate the more timely and cost effective completion of dental procedures and subsequent healing by cleansing away the accumulated tissue damage and infectious debris in a manner that supports the natural repair process in oral tissues.

The Limitations of Current Standard Dental Therapeutic Techniques

The bottom line with dental treatment procedures is that the cleaner you can make a diseased area of tissue and the longer you can maintain it that way, the more successful you will be in stopping any ongoing destruction and the more likely it will be that the tissue will heal. The currently accepted standard professional dental procedures are all somewhat mechanically limited in their ability to eradicate diseased tissue and the offending bacteria at the molecular level. These limitations are presented in separate categories immediately below.

1) The limitations of mechanical dental cleaning methods

There are a variety of well-known standard mechanical approaches to the professional removal of dental plaque including methods such as manual scaling and powered ultrasonic scalers. Dental plaque biofilm has physical properties that can make effective mechanical removal time consuming. Plaque has extreme visco-elastic characteristics such that it binds tenaciously to the surfaces of hard tissues and cannot be easily detached and washed away completely with oral rinses alone but usually requires application of mechanical shear forces. The supragingival and subgingival anatomy of the tooth adds to this problem as it often contains areas that may be covered by plaque but with limited physical access for applying a mechanical technique. As a consequence of the extreme adhesive properties of plaque and the limitations created by tooth anatomy it is often impossible to adequately remove plaque biofilm from teeth using mechanical techniques alone. Some mechanical techniques simply smear the plaque around on the tooth surface while not removing much of it.
Essentially all currently used professional methods are less than totally satisfactory for the simple reason that plaque biofilm pieces generated by mechanical shear force still contain viable microbes. While most pieces of viable plaque biofilm that are liberated are removed by rinsing, some viable attached pieces remain behind. These residual pieces readily seed the re-establishment of plaque.

2) The limitations of antiseptics and antibiotics
Antiseptic oral rinses and topical antibiotics have limited efficacy against the bacteria living within dental plaque biofilm. One of the most important features of microbial biofilms is that the microbes that live within them are known to be generally resistant to the action of typical antiseptics and antibiotics. There are many reasons offered in the scientific literature for this non-specific resistance. The critical fact is that these agents must be used at much higher concentrations and for much longer periods of time to

kill microbes living in oral biofilms than to kill microbes living outside of biofilms. This has greatly limited their usefulness in the treatment of common oral diseases that originate from plaque biofilm microbes. A related concern is that an antiseptic or drug may initially be somewhat effective against biofilm microbes, but using it for an extended time at high concentrations will lead to emergence of specific drug resistance that could spread rapidly due to the proximity of the bacterial colonies that cohabitate in a plaque biofilm.
It is also critical to remember that antibiotics and antiseptics are fundamentally limited in efficacy because they only attack the microbes themselves and they do nothing to eradicate the plaque matrix. Failure to eradicate the plaque matrix increases the risk of recurrent disease through reformation of viable plaque biofilm bacterial colonies. They also do nothing to reduce the risk of ongoing inflammation through removal of tissue debris and other inflammation triggers.

3) Limitations of common dental agents
There are a variety of agents that are commonly used in dental procedures to prepare tissue surfaces for restorations, bonding or sealing procedures. Among these are solutions of phosphoric acid, EDTA, citric acid, alcohols, volatile organics, surfactants, antiseptics, antibiotics and sodium hypochlorite (bleach). It has been demonstrated that all of them have limited ability to eradicate plaque biofilm and biofilm bacteria except for the sodium hypochlorite solutions. Hypochlorite solutions have had very limited use in plaque removal procedures however due to the fact that through inadvertent contact they can rapidly damage normal healthy oral tissues.

3) The limitations of uncommon methods
There are two techniques currently being marketed for the treatment of infection and inflammation in the mouth that have yet to become widely used. One is the soft-tissue laser technique and the other is the photo-dynamic therapy technique.
The soft tissue laser uses heat generated by laser energy to destroy plaque biofilm and necrotic tissue. This technique is thought to have not gained much popularity because it requires a substantial investment in equipment, a substantial investment in training and is not without risk of harming healthy tissue. It suffers some of the same challenges as the standard mechanical techniques in that the laser may not be able to access all of the surfaces that are covered with biofilm or dead tissue.
Photo-dynamic therapy refers to a technique wherein a light activated non-specific antimicrobial agent is placed in contact with an infected surface where it is absorbed by microbes. A specific light frequency is delivered by a fiber optic device to activate the antimicrobial agent and kill the microbes. This method has the same limitations of standard antiseptic and antibiotic agents in that it does not do anything to remove biofilm matrix or inflammatory debris.

4) The limitation of methods that are currently in development
There is ongoing research to develop new antiseptic agents and antibiotics that can overcome the resistance of plaque microorganisms. As explained earlier, it is now understood that thousands of different species of bacteria colonize the oral cavity and that the vast majority of them have never been studied in a laboratory. It has not yet even been determined how to isolate and grow these bacteria in a laboratory so that their metabolism can be studied and their potential role in dental disease determined. Without this information it is difficult to say that any particular antiseptic or antibiotic will be ultimately effective in the treatment of dental disease because there may be many more untested pathogenic bacteria in the oral cavity that have simply not yet been identified as such. The work of identifying all of these agents and developing drugs to control them will likely require many years and an incalculable amount of resources. This makes the research into the development of alternative antibiotics and antiseptics impractical at this point in time.
It has been proposed that a simpler approach for developing a method to control oral bacteria is by aggressively studying the mechanisms by which plaque biofilm is formed since the majority of oral bacteria live in biofilms. This research process has suffered from the same types of problems that are found in other antiseptic and antibiotic research, namely, there are simply too many different species present and they appear to all use somewhat different mechanism to regulate their behavior in a biofilm environment. The goal of producing products which are effective at stopping biofilm formation

specifically by disease-causing bacteria appears to be impractical at this point.

Exceptional Opportunities to Change Dentistry with HYBENX

The properties of HYBENX products and the benefits that they provide in the treatment of dental disorders are unique. There are some clinical situations where application of a HYBENX product has the potential to fundamentally change the way that a professional dental treatment method is performed. Several examples are provided here.

1) Oral Ulceration and Mucositis

Ulceration and inflammation of the oral mucosa is usually treated with a variety of topical agents that are designed to provide temporary relief of pain and discomfort while the lesions heal. These products typically must be applied repeatedly throughout each day for 7-10 days.

HYBENX products can be used to instantly relieve the pain and discomfort of mucosal inflammation and ulceration in a single application. The products are applied with a swab to the damaged area for only 5 – 10 seconds and then the lesion is rinsed with water. When HYBENX contacts damaged and infected tissue on a mucosal surface it instantly desiccates it to the point where it denatures and coagulates the debris and fragile tissue structures. This coagulation process in effect instantly converts the damaged tissue debris into a membranous layer of dense denatured disinfected tissue. This layer then acts as a protective barrier that prevents microbes from re-infecting the area of the lesion and prevents environment irritants from causing more pain. Occasionally a dental patient may defer completion of a routine dental procedure due to the pain of a mucosal lesion. A practitioner can now provide relief from that pain within seconds by using HYBENX Technology.

2) Endodontics

HYBENX can be used to completely remove the smear layer (biofilm) in the root canal during preparation for capping. In addition, HYBENX reduces bleeding and weeping which interfere with proper sealing of the canal.

3) Subgingival Cleaning in Minimally Invasive Periodontal Therapy

Subgingival cleaning is the primary technique used in the treatment of periodontitis and in the maintenance of periodontitis patients. Periodontitis is a disease where the tissue that connects the root of teeth to the jaw bone is destroyed by an inflammatory reaction to bacteria in the area. The destruction of the tissue creates a space between the tooth and gum tissue referred to as the periodontal pocket. In periodontitis this space becomes filled with necrotic tissue debris, blood and infectious microbes. The methods for treating this disease requires that the pocket by cleansed of the dead tissue and microbes so that it can heal. This is usually done by a mechanical procedure that is referred to as scaling and root planning (SRP). Antiseptic and antibiotic solutions are sometimes also applied to the pocket to suppress growth of bacteria. SRP is usually effective in milder cases of periodontitis where destruction of the tissue in the pocket has not extended very far. SRP is much less effective in cases of more severe tissue destruction where the pockets are deeper because the mechanical techniques become more difficult to perform and require more time to do well.

Application of HYBENX products could potentially change the way that periodontitis treatment is performed by chemically doing much of the cleansing that is now done mechanically. When a periodontal product is irrigated to overflowing with a HYBENX product many beneficial things happen in the pocket. Everything that triggers or promotes inflammation will be desiccated, denatured and detached from the pocket surfaces so that it can be easily rinsed away. This includes microbes, blood, necrotic tissue, white blood cells and any other inflammatory mediators. Open tissues are coagulated over and sealed. Edema is reduced and as a result the gum tissue is tightened around the tooth root. Pre-SRP HYBENX irrigation together with post-SRP HYBENX irrigation minimizes the amount of mechanical scaling and mechanical trauma that has to be delivered to the periodontal pocket in order to achieve a therapeutic result. Treatment procedures are completed more quickly and patients have less discomfort when the anesthetic wears off.

Another fact to consider is that effective performance of SRP requires significant training and clinical experience. This is especially true in the case of severe periodontitis where the pockets are deeper.

Subgingival cleaning that is supplemented by adjunctive applications of HYBENX does not require as much training, as much experience or as much effort to be just as effective, even in the case of deep pockets, because most of the cleansing work is done by the HYBENX product and does not depend on the manual scaling technique and experience of the practitioner.
Finally, in cases of peri-implantitis, HYBENX is particularly effective in debriding plaque from the irregular complex metal surfaces of both sub- and supra-gingival restorative structures.

4) Using HYBENX to Improve Infection Control Procedures

Infection control policies involve the implementation of procedures specifically designed to reduce the risk of spreading infectious diseases between patients and staff. Typically, many infection control methods are utilized in every dental practice including such things as mandatory use of gloves, wearing surgical masks and frequent cleaning of all clinic surfaces. These various methods are considered to work in concert with each other. Each one is viewed as an additional "layer" of protection. The decision as to whether or not any specific additional layer of infection control should be added to a clinical practice depends on the cost/benefit analysis for that layer. HYBENX products are inexpensive and easy to apply. They require no additional equipment or specialized training. They can be used to completely and instantly eradicate all microbial pathogens from any surface in the oral cavity where a dental procedure is to be performed thereby eliminating any risk of spreading pathogens during the procedure. An application of HYBENX to the same area after a procedure is completed eliminates the risk that pathogens were spread into that site by the practitioner.

5) Using HYBENX in Prophylactic Supragingival Cleaning and Preventive Care

Routine supragingival cleaning and polishing of teeth are a critical part of preventive dental care. However, reimbursement for these procedures is usually limited and fixed which means that it is important to do this work in the most cost-effective manner possible. HYBENX is most useful when doing preventive care procedures on individuals with significant plaque and calculus on their teeth. A simple brief focal application of HYBENX to the surface of dental plaque will cause it to quickly detach from the tooth surface making it easier to remove. The structure and attachment of calculus deposits are also disrupted by HYBENX so that they are much easier to remove after treatment. In other words, the more significant the plaque and calculus deposits are, the more useful HYBENX is as an adjunctive agent.

6) Using HYBENX in Cavity Disinfection in Minimally Invasive Caries Restoration

Cavities are caused by bacteria living in plaque on the surface of teeth when they metabolize certain carbohydrates and secrete organic acid waste products onto the tooth surface. The acid erodes the enamel mineral from the surface to the point where the dentin inside the tooth is exposed. This in turn allows the biofilm to expand into the interior of the tooth where the acid starts to erode the mineral of the dentin and softens it.
The repair of a tooth cavity requires that the infectious biofilm material that is causing the disease to be destroyed and mechanically removed from the interior dentin. In addition, the damaged dentin is supposed to be mechanically removed so that whatever material is used to fill the cavity can bond to solid healthy undamaged dentin and not to soft necrotic tissue. A major concern when performing the mechanical removal of diseased dentin has to do with how much material must be removed to have a successful outcome. Removing too little creates a risk that the restoration will fail due to persistent infection or re-infection. Removing too much creates a risk of iatrogenic exposure of the tooth pulp and subsequent pulpitis as well as a risk of simply damaging the structural integrity of the tooth to the point where the tooth is easily cracked by mechanical stress. These concerns have caused some to advocate for the development of so-called minimally invasive caries restoration techniques. The idea is that these techniques would utilize a minimum amount of mechanical dentin removal to lower the risks of pulp exposure and structural damage and would use some other means to eradicate the biofilm infection in the dentin and firm up the dentin tissue for bonding.

7) Use of HybenX® in implant surgery

Before inserting the implants once the bone is regularized, if the flap technique is performed, we apply HybenX® to ensure the absence of bacterial load. With the flapless technique, we can clean the soft tissue before using the punch and after using the implant, use HybenX® in the osteotomy. In immediate or delayed post-extraction implants, we can

decontaminate the socket prior to implant insertion, thus ensuring that the risk of infection due to the presence of biofilm in the socket is avoided.

To eradicate the biofilm before the associated use of biomaterials or autologous bone.

8) Use of HybenX® in prosthodontics and maintenance of prostheses on implants

The use of HybenX® can help us from the impression taking to avoid bleeding due to its hemostatic property as well as prior to the cementing of the prostheses and in the maintenance of the screwed prostheses, guaranteeing with their application the elimination of the biofilm.

Peri-implant mucositis is inflammation of the tissues surrounding the dental implant and represents the most frequent complication in implantology. Although its prevalence is variable, according to studies we can say that it affects between 30% and 50% of patients with implants.

Peri-implantitis is always preceded by mucositis. This is characterized by, in addition to the inflammation of the gum surrounding the implant, a loss of bone that supports the implant, and may even cause the loss of the latter. If the patient is a prosthetic wearer, it will move and become out of adjustment causing numerous discomforts.

9) Use of HybenX® in orthodontics

For the maintenance of fixed brackets and retainers, eliminating biofilm and plaque.

A few basic tips from Users to improve your HYBENX® Product Experience

Surface Preparation
Note that HYBENX® Products effectiveness is diminished by the presence of water or other liquids such as blood. Try to blot or air dry the surface prior to application. In cases of excess bleeding, HYBENX® Product should be applied more liberally to take advantage of its hemostatic effect to thoroughly cleanse the treated tissue surface.

Less is more
Clinicians who use antibiotics and cleansers often feel that "more" and/ "longer" is better. This is not the case with HYBENX® Products. Their cleansing action is almost instantaneous. It is better to leave product in place for a shorter time such as 20-30 seconds, prior to rinsing with vacuum aspiration. A second short application can still be used if necessary to finish cleansing and sealing the tissue site if more invasive mechanical cleaning is deemed necessary.

Soft tissue Appearance
One should expect an immediate graying or lightening of the tissue coloration post-treatment. This is due to the desiccation of the superficial layer of the mucosal tissue. The tissue is not damaged and will return to its normal pink coloration within days.

Sensitivity
In some tissue sites, HYBENX® Products can cause a stinging sensation upon application. Further, occasionally local residual sensitivity will persist for a day or so after more aggressive treatment procedures. These are within the normal range of expected responses and will diminish within hours to days.

HYBENX® Products Bibliography

Endodontics

Abud-Blanco, K, L Bustos-Blanco, E Covo-Morales, and L C Fang-Mercado. *Actividad Antimicrobiana de los compuestos fenólicos sulfonados en el sistema de conductos radiculares. Revisión Sistemática. Article in Spanish; Translation of title: Antimicrobial activity of sulfonated phenolics components in the root canal system. Systematic review.* Rev CSV. **7**(2): 53-60. 2015.

Rohrer, MD, HS Prasad, and E Savord. *A Histological Assessment of a HYBENX® Oral Tissue Decontaminant in Vital Pulp Therapy in Dogs*. J. Biol. Regul. Homeost. Agents. Apr-Jun: 30(2 Suppl 1): 189-97. 2016.

The authors demonstrate that vital pulp exposures, treated with **HYBENX® Oral Tissue Decontaminant**, demonstrated significant improvements in new dentin formation and tooth vitality when compared to the conventional standard of care.

General Dentistry

Ioannidis, AB, B Stawarczyk, B Sener, T Attin, and PR Schmidlin. *Influence of dentin and enamel pretreatment with acidic sulfur compounds on adhesive performance*. Clin. Oral Invest. **17**(8): 1885-92. 2013.

Authors concluded that **HYBENX® Oral Tissue Decontaminant** did not have a deleterious etching effect on enamel or dentin. Enamel still requires conventional etching procedures for bonding resins. Bonding to dentin was enhanced by pre-exposure to the **HYBENX®** Solution.

Argüello, Claudia. *A better way to remove the disease-causing Periodontal and Peri-implant Oral Biofilm*. Dental Tribune **3**(9): 10-13. 2014. *(Translated from the original Spanish text)*.

Author summarizes the history, etiology, and health ramifications of oral biofilm. She explains the **HYBENX® Oral Tissue Decontaminant** technology and recommends that the product be used adjunctively by the dental clinician to treat periodontal disease and peri-implantitis.

Nardi, GM, S Sabatini, F Scarano, and M Petruzzi. *Effectiveness of a new chemical agent for topical use in the treatment of a patient with aphthous major ulcers.* Poster Presentation at the National Congress of the Faculty of Dentistry, University of Rome, April 18-20. 2013. (*Translated from the original Italian text).*

Authors concluded that immediately after treatment with **HYBENX® Oral Tissue Decontaminant**, patients were symptom free and experienced complete healing of the ulcer surface.

Periodontology

Bracke, JW, M Basara, E Savord, A Dunaway, MJ Watkins. *Pilot Evaluation of a Simple Adjunctive Method for Improved Removal of Oral Biofilm during Conventional Scaling and Root Planing Therapy*. J. Biological Regulators and Homeostatic Agents. Vol. 29, no. 3 (S1): 6-9. 2015.

Authors describe a simple adjunctive topical method for removing biofilm from tissue surfaces at the molecular level using **HYBENX® Oral Tissue Decontaminant** solution. Bacterial DNA pyrosequencing and inflammatory mediator immunoassays were used as surrogates for assessing cleaning efficacy.

Isola, G, G Matarese, RC Williams, VI Siciliano, A Alibrandi, G Cordasco, and L Ramaglia. *The effects of a desiccant agent in the treatment of chronic periodontitis: a randomized controlled clinical trial*. J Clin Oral Invest 17 June (doi:10.1007/s00784-017-2154-7). 2017.

Authors conclude that SRP plus the desiccant (**HYBENX® Oral Tissue Decontaminant**) resulted in a greater reduction in clinical, microbial and inflammatory mediators compared to SRP alone and demonstrated a significant approach to control the levels of certain periodontal pathogens and inflammatory mediators in patients with CP.

Independent Review of the above Isola Paper: Brignardello-Petersen, R. *A Desiccant Agent as an Adjuvant to Scaling and Root Planing Improves Clinical Parameters in Patients with Chronic Periodontitis and Good Prognosis up to 1 Year after Treatment.* JADA June 17, 2017.

Author agreed with the validity of the controls used in the above RCT and indicated that the product showed merit up to the one-year follow up data point.

Lauritano, D, G Ambra, and F Carinci. *The Efficacy of **HYBENX® Oral Tissue Decontaminant** for Periodontal Disease Treatment: A Case Series Study*. International Journal of Advances in Case Reports; 2(7): 405-408. 2015.

Authors evaluated periodontal pockets in 11 patients using bacterial DNA analysis before and after HYBENX treatment. They observed a statistically significant reduction in red complex microorganisms at 15 days post treatment. They conclude that 1) HYBENX is an effective adjunct to eradicate bacterial loading in the pockets of patients affected by periodontitis and 2) HYBENX is an efficacious medical device for use in the management of moderate to severe chronic periodontitis.

Nardi, GM, S Sabatini, and FR Grassi. *Effectiveness of a chemical decontaminant (**HYBENX® Oral Tissue Decontaminant**) in the reduction of bleeding at hypersensitivity and in improving patient comfort.* Poster Presentation at the National Congress of the Faculty of Dentistry, University of Rome, April 18-20. 2013. *(Translated from the original Italian text).*

Authors concluded that bleeding on probing and dentinal hypersensitivity were improved in the treated cohort. Periodontal probing depth and plaque indices were also improved but did not reach statistical significance under the conditions evaluated. Patients preferred the treatment protocol versus the control (no decontamination treatment).

Nardi, GM, S Sabatini, D Lauritano, C Denisi, and FR Grassi. *Management of biofilm control in an elderly patient suffering from rheumatoid arthritis: a case report*. International Journal of Immunopathology and Pharmacology **26**(4): 973-6. 2013.

Authors concluded that the use of **HYBENX® Oral Tissue Decontaminant,** as an adjunct during remediation of periodontal disease, greatly facilitated ease of cleaning and patient comfort.

Lombardo, G, A Pardo, A Fiorino, G Corrocher, and G Urbani. *Full-mouth ultrasonic debridement in associazione a HYBENX nell'approccio iniziale al trattamento della parodontite cronica. (Full-mouth ultrasonic debridement in association with **HYBENX® Oral Tissue Decontaminant** as an initial approach to the treatment of chronic periodontitis)*. Quintessence International (Periodontology) **28**(3): 5-14. 2012.

36 patients with 393 periodontal defects were treated with full-mouth ultrasonic debridement either with, or without **HYBENX®** Solution as an adjunctive therapy. At 3 months followup, the **HYBENX** cohort was significantly improved over control. In particular, BOP in deep pockets (PPD> 7 mm) was reduced from 89 to 41% versus 90 to 63% in the control group (p = 0.0168). Authors concluded that **HYBENX® Oral Tissue Decontaminant** is a valuable aid to the initial treatment of chronic periodontitis.

Lombardo, GA, C Signoretto, G Corrocher, A Pardo, J Pighi, A Rovera, F Caccuri, and PF Nocini. *A topical desiccant agent in association with the ultrasonic debridement in the initial treatment of chronic periodontitis: a clinical and microbiological study*. New Microbiology **38**(3): 393-407. 2015.

In this randomized, split-mouth, single-blind prospective clinical study, the authors observed significant improvements in clinical outcomes at three months post-treatment in patients treated with adjunctive **HYBENX® Oral Tissue Decontaminant** therapy when compared to patients treated only by ultrasonic debridement. In particular, a significant reduction in the levels of anaerobic microflora and gingival inflammation was noted.

O'Hehir, TE. *A clinical practice observation of the effects of **HYBENX® Oral Tissue Decontaminant** plus instrumentation on non-responding periodontal sites by dental hygienists in the European Union*. Hygiene and Prevention: Profile in Oral Health, October: 122. Dentaltown.com. 2011.

Pilot clinical trial evaluation of patients in England, Scotland, and Italy using **HYBENX® Oral Tissue Decontaminant** as an adjuvant in scaling and root planning. Author concluded that this treatment reduced pocket depth in 10 of 13 patients with non-responding pockets greater than 5mm at the six-week follow-up analysis.

Pini-Prato G, C Magnani, and R Rotundo. *Treatment of Acute Periodontal Abscesses using the Biofilm Decontamination Approach. A Case Report Study*. Int J Periodontics Restorative Dent. 36(1): 55-63. 2016.

Authors conclude that the biofilm decontamination approach using **HYBENX® Oral Tissue Decontaminant** seems to be a very promising technique for the treatment of acute periodontal abscesses without using systemic or local antibiotics.

Sahni K, Khashai F, Forghany A, Krasieva T, and P Wilder-Smith. *Exploring Mechanisms of Biofilm Removal*. Dentistry 6(4): 371. 2016.

Authors demonstrate the removal of biofilm from extracted teeth using **HYBENX® Oral Tissue Decontaminant**.

Peri-implantitis

Lavere, E, Z Rifkin, L Mikulski, and S Andreana. *Antimicrobial Effects of a Root Canal Cleanser in Treating Contaminated Implants*. Ex Vivo Study. IADR Poster Session. Boston. 2012.

Authors concluded that the use of **HYBENX® Oral Tissue Decontaminant** "can serve as a beneficial form of treatment against peri-implantitis and subsequent infected implant defects not only due to its efficacy in halting bacterial growth, but as well as its non-invasive capabilities during application".

Lombardo G, C Signoretto, A Pardo, G Corrocher, J Pighi, A Signoriello, and Nocini PF. *Topical Desiccant Agent in Association with Manual Debridement in the Initial Treatment of Peri-implant Mucositis: A Clinical Prospective Study*. EuroPerio9, Amsterdam, Poster. June 20-23, 2018.

Authors compared the effectiveness of the use of **HYBENX® Oral Tissue Decontaminant** ("HOTD") vs. Chlorhexidine ("CHX") in reducing peri-implant mucositic inflammation. They concluded that HOTD was superior in reducing PPD but that CHX was superior in reducing the level of anaerobes.

Lombardo G, G Corrocher, A Rovera, J Pighi, M Marincola, J Lehrberg, and PF Nocini. *Decontamination Using a Desiccant with Air Powder Abrasion Followed by Biphasic Calcium Sulfate Grafting: a New Treatment for Peri-Implantitis.* Case Reports in Dentistry. 2015.

The authors noted after two-year follow up that the use of **HYBENX® Oral Tissue Decontaminant** and air powder abrasives, followed by bone defect grafting, represents a viable option in the treatment of peri-implantitis.

Lopez MA, M Andreasi Bassi, L Confalone, F Silvestre, and C Arcuri. *The Treatment of Peri-Implant Diseases: A New Approach Using HYBENX® as a Decontaminant for Implant Surface and Oral Tissues*. ORAL & Implantology 9(3):106-114. 2016.

Authors conclude that the use of **HYBENX** significantly reduced: 1) the need for invasive surgery, 2) bacterial load, 3) patient discomfort, 4) healing time, and, 5) the need for antibiotics, yielding a clear clinical improvement in both mucositis and severe peri-implantitis.

Mancini EA and GP Pini Prato. *Procedimiento de decontaminación del biofilm para el tratamiento del absceso periodontal agudo y la periimplantitis. [TRANS: The biofilm decontamination approach for treatment of periodontal abscess and peri- implantitis]*. Rev Asoc Odontol Argent 104(2): 79-85. 2016.

Authors conclude that the biofilm decontamination approach, using **HYBENX® Oral Tissue Decontaminant**, is a very promising technique for the treatment of acute periodontal abscess and peri-implantitis without the use of systemic or local antibiotics.

Pini-Prato G, C Magnani, and R Rotundo. *Nonsurgical Treatment of Peri-implantitis Using the Biofilm Decontamination Approach: A Case Report Study*. Int J Periodontics and Restorative Dent. 36(3): 383-391. 2016.

Authors conclude that the biofilm decontamination approach using **HYBENX® Oral Tissue Decontaminant** seems to be a very promising technique for the treatment of peri-implantitis in a short-term evaluation without using systemic or local antibiotics.

Reif-Bankmann, Sabine. *Long-term success of implant restorations through professional therapy concepts*. J. Dental Hygiene **1**: 14-18. 2013.

Author concludes that successful hygienic intervention in mucositis associated with peri-implantitis requires the use of an adjunctive debridement material such as **HYBENX® Oral Tissue Decontaminant** in combination with standard manual or mechanical debridement procedures.

Solakoglu, Önder. *Treatment of peri-implantitis - a protocol for clinical success*. Zahn Prax **14**(6): 306-315. 2011. (*Translated from the original German text*).

Author indicates that the most critical step in the successful surgical restoration of severe peri-implantitis is effective decontamination of the implant surfaces with a material such as **HYBENX® Oral Tissue Decontaminant** to completely remove biofilm.

Oral Aphthous Ulcers

Lauritano, D, M Petruzzi, GM Nardi, F Carinci, G. Minervini, D Di Stasio, and A Lucchese. *Single Application of a Dessicating Agent in the Treatment of Recurrent Aphthous Stomatitis*. J. Biological Regulators & Homeostatic Agents
Vol. 29, no. 3 (S1): 59-66. 2015.

Nardi, GM, FR Grassi, D Lauritano, and M Petruzzi. *An Alternative Approach for the Treatment of Major Aphthosis: Case Report*. J. Interdiscipl. Med Dent Sci **2**(5):

3pp. 2014.

Authors conclude that **Oralmedic® Barrier Solution** was safe and effective for the treatment of severe recurrent oral ulcers using weekly topical applications for four weeks.

Porter, SR, K Al-Johahni, S Fedele, and DR Moles. *Randomized controlled trial of the efficacy of **HYBENX® Oral Tissue Decontaminant** in the symptomatic treatment of recurrent aphthous stomatitis.* J. Oral Disease **15**(2): 155-61. 2009.

Treatment of oral ulcers with **HYBENX®** Solution safely, effectively, and more quickly, reduced the painful symptoms of RAS when compared to the leading alternative treatment.

Veterinary Periodontology

Klima, Larry J Et al. *Use of **HYBENX® Oral Tissue Decontaminant** as a topical treatment in gingivoplasty in a boxer dog: a case study.* (Unpublished internal report, EPIEN Medical Inc.).

Authors found **HYBENX®** Solution dramatically reduced bleeding during surgery and enhanced patient management.

Other Unpublished Data:

Costerton, JW and C Shaudinn. *Studies on the effect of **HYBENX® Oral Tissue Decontaminant** on Biofilm in the PerioChip and Root Canal models, as well as freshly extracted human teeth*. 2007.

Authors observed complete obliteration of mature biofilm after a two-minute exposure confirmed by live/dead staining confocal and electron microscopy.

Huber, BJ, DVM**,** Diplomate, American Board of Veterinary Practioners. American Hospital of Rowlett & Diagnostic Center, Rowlett, TX. *Testimonial, Internal Report, EPIEN Medical Inc.* 2013.

*We are routinely obtaining better outcomes using **HYBENX®** Products in dental cleaning procedures for improved pain management and hemostasis and removal of inflamed mucosal tissue in stomatitis patients.*

Klima, LJ, DVM**,** Diplomate American Veterinary Dental College. Comprehensive Oral Care and Maxillofacial Surgery Clinic, Ft. Collins, CO. *Testimonial, Internal Report, EPIEN Medical Inc*. 2013.

*We are routinely using **HYBENX®** Solution for treatment of periodontal pockets, furcational defects, stomatitis and mucositis lesions, gingivoplasty, and general patient case management.*

Nielsen, David, DVM**.** Veterinary Dentist. Animal Medical Centers of California and South Dakota. *Testimonial: Internal Report, EPIEN Medical Inc.* 2013.

*We are routinely using **HYBENX®** Solution for cleaning, root canal cleansing, severe periodontitis, and in feline aggressive stomatitis.*

Davis, SC, D Chagui, Y Rivas, and E Gonzalez. *Pilot Study Report: Evaluation of the Effect of Antimicrobial Agents on the Proliferation of Acinetobacter baumannii, Pseudomonas aeruginosa, and Methicillin Resistant Staphylococcus aureus in Deep Partial Thickness Wounds using a Porcine Model*. (University of Miami Miller School of Medicine Contracted research, *Internal Report, EPIEN Medical Inc*). 2006.

***HYBENX®** Test Solutions exhibited strong antimicrobial activity in this preliminary pigskin infection model assessment.*

Berman, B, OA Perez, S Konda, and J K Patel. Antifungal Effect of **HYBENX®** Solution in an In-vitro Model of Fungal Infection. (University of Miami Miller School of Medicine Contracted Research. *Internal Report, EPIEN Medical Inc*). 2007.

HYBENX® Solution demonstrated antifungal activity in a human skin model system (Apligraf®).

US Customer NOTICE: HYBENX® Product is cleared in the US on a 510(k) HYBENX® Root Canal Cleanser for use on the interior surfaces of the tooth root canal. As such, it is deemed safe and effective on internal nerve, bone, and dentinal structures. The EU has approved the product more broadly as a Class I Medical Device for unrestricted oral cleansing

applications. EPIEN Medical does not promote the product for those broader applications in the US. However, the authors above deem HYBENX to be safe for use on all oral surfaces per the published applications.

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