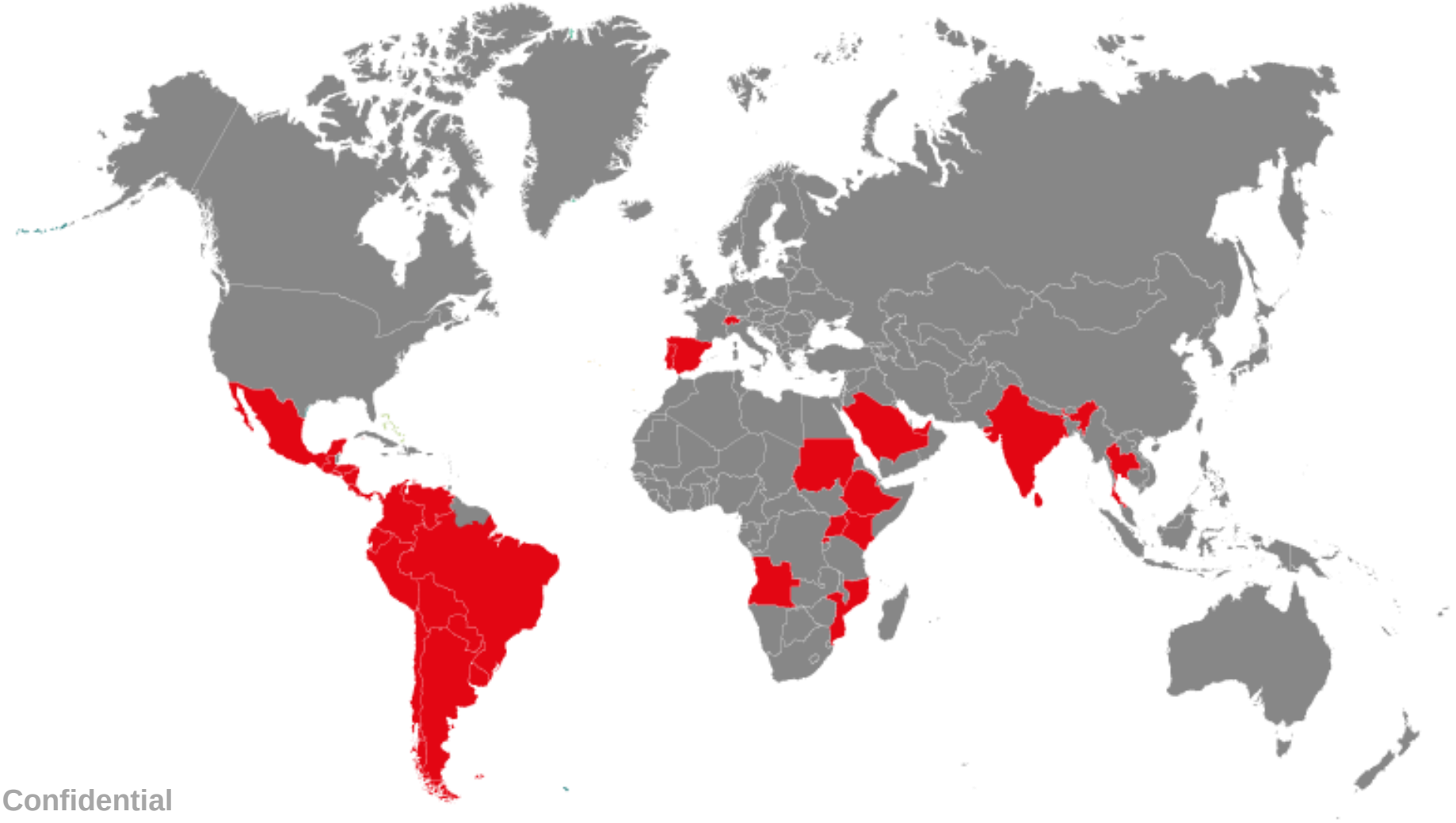
# BRIX3000®

Gel for atraumatic removal of caries.

# Brix 3000 presence in Latin America, Africa and Europe (2016)



## CE mark and FDA

Currently the laboratory Brix Medical Science is in the process of certification of ISO 13.485 corresponding to the pharmaceutical industry, having already passed the first two reviews conducted by international consultant DNV GL qualification and certification of ISO standards among other things.
After obtaining this standard, we will process the CE mark and FDA, estimated to have those qualifications in April/May 2017.

# Product presentation

In septembe 2016, Brix 3000 will introduce a new packaging container of 3 ml. It is an ecological recyclable aluminum tube with low environmental impact (Low CO2).

# BRIX3000®

Gel for atraumatic removal of caries.

# E.B.E. Technology characteristics:

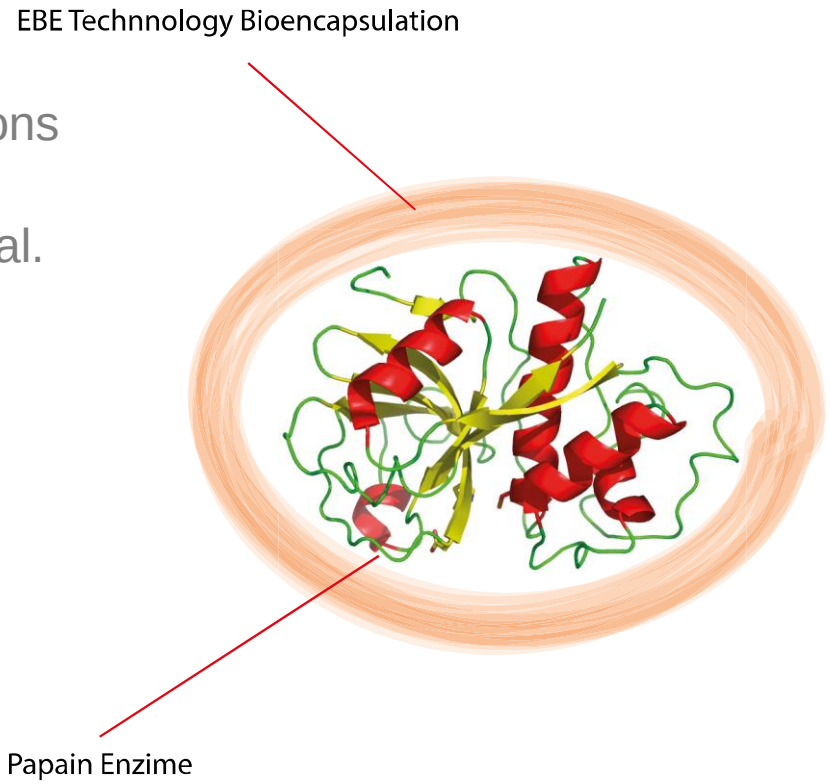
This new technology, changed the concept of encapsulation of enzymes and release high objective concentrations in topical products.

1. **It allows high concentrations of enzymes.**
2. **It allows an increase of the enzyme protealysis.**
3. **It requires no refrigeration**
4. **It reduces the time of necrotic tissue removal.**
5. **It is non traumatic.**
6. **Makes the enzyme has optimus selectivity.**
7. **E.B.E. Technology is an exclusive patent of Brix USA LLC.**

# E.B.E. Technology characteristics

*It allows high concentrations of enzymes.*

E.B.E. Technology allows concentrations of 3000 U/mg of enzyme, widely surpassing the current papain technical.



# The Enzyme gel and the EBE Technology

This gel is a dental product for non-traumatic caries treatment involving an enzymatic activity ( 3.000 U/mg*) in which the papain is bio-encapsulated by using **E.B.E. Technology (Encapsulating Buffer Emulsion)** exclusive technology that immobilises and confers stability, which increases the enzymatic activity of the final product exponentially with respect to current technology. Thus, the following is achieved: higher proteolysis effectiveness to remove collagen tissue in decayed tissue, less dissolution of active principle by oral fluids, greater resistance to storage  even in unfavourable conditions, without requiring cold-chain preservation, and greater antibacterial and antifungal potency with an increase in antiseptic effect on tissue.

# Introduction

Papain is a similar endoproteína to human pepsin, which has bactericidal, bacteriostatic and anti-inflammatory, from the latex of the leaves and fruits of mature green papaya, Carica papaya, grown in tropical countries such as Brazil, India, Ceylon , South Africa and Hawaii. In relation to other natural enzymes, papain has some advantages such as: quality and enzymatic activity; stability under adverse conditions of temperature, humidity and atmospheric pressure; being in high concentration in the extracted latex shell containing papaya and a high commercial value due to the diversity of uses presented.

# Classification of medical product

BRIX 3000 manufactured by Brix S.R.L. of Argentina, it has been classified as Medical Devices Class II, in accordance with Rule 6 of Annex II of Disposition of ANMAT 2318/2002:

All surgically invasive medical devices intended for transient use are in Class II unless:

- Specifically intended to diagnose, monitor or correct a heart or circulatory system center by direct contact with these parts of the body, in which case impairment will be included in Class IV.
- Reusable surgical instruments, in which case they are in Class I.
- They intended to supply energy in the form of ionizing radiation in which case they are in Class III.
- Intended to have a biological effect or to be absorbed completely or largely, in that case there are in Class III.

# Classification of medical product

Brix SRL Argentina, complies with the requirements established by ANMAT in their Good Manufacturing Practices for Medical Devices (BPF).

The Risk Management Document was prepared in accordance with the guidelines of the ISO 14971:2007 norm.

# Life and validity of the medical product

BRIX 3000 life/validity is determined in 48 months from the date of preparation of each batch produced.

The expiry date of the each package is clearly spelled out in the box and product packaging.

# Health ratings

**Brix3000** gel contains excipients authorized by **ANMAT** (Argentine Administration of Drugs, Food and Medical Devices) and **INVIMA** (National Institute of Food and Drug Monitoring) of Colombia, **ANVISA** (Agência Nacional de Vigilância Sanitária) of Brasil, and **ARCSA** (Agencia Nacional de Regulación, Control y Vigilancia Sanitaria) of Ecuador.

**ANMAT** (Argentina): PM2177-1

**INVIMA** (Colombia): 2016DM-0014266

**ANVISA** (Brazil): REG. ANVISA 80853390008

**ARCSA** (Ecuador) 2099-DME-0816

Also in the process of health registration in Mexico, Ecuador, Costa Rica, Peru, Bolivia, Guatemala, Nicaragua, Honduras, Chile, Paraguay, Venezuela, Panama, El Salvador.

# Health ratings

The laboratory Brix SRL of Argentina, is currently in the process of implementing the norm ISO 9001/13.485, process completed by December 2016.

In addition, we are in the process of obtaining CE mark (European Community) granted by the European Medicines Agency (EMA) estimating get to the end of 2016.

Also, we are in the process of obtaining FDA clearance for the manufacturing process of our products (end of 2016).

We have made an inquiry of product classification in Europe through the Spanish laboratory Lacer. We are awaiting of the response.

# Safety and effectiveness

**Brix 3000** holds dermatological certificates attesting to the non-toxicity of the product to mouth, skin or eyes, and demonstrating that it does not provoke any type of reactions when it comes into contact with healthy tissue.

# Study irritability in eyes:



EDYAFE
Tecnología y experiencia a su servicio

Laboratorios Biomic S.R.L
Valentín Virasoro 1073
(1405) Buenos Aires - Argentina
Tel/Fax: 4982-0329 (Línea rotativa)
e-mail: info@biomic.com.ar
website: www.biomic.com.ar

Sistema de Gestión de Calidad ISO 9001:2008 acreditado por el Bureau Veritas con acreditaciones que lo respaldan

(Para corroborar la autenticidad del presente ingrese esta clave en nuestra página Web: 1CzGB7CGKS )

PROTOCOLO Nº **83226** Hoja 1 de 2

Buenos Aires, lunes, 15 de septiembre de 2014
Remitente: Brix SRL
Muestra Declarada: BRIX 3000 PLUS
Identificación: Lote: 20140724 100 Vto: 24/07/2016
Solicita: Índice de irritación en mucosa ocular (cod.: 463)
Fecha Inicio de Ensayo: 8/9/2014 Fecha de terminación del ensayo: 15/09/2014
Nota: El muestreo fue realizado por el remitente.

**METODOLOGÍA:**

Preparación de la muestra: Sin diluir.
De acuerdo al Test de J. H. Draize, se uso nueve conejos albinos divididos en dos grupos. Al primer grupo de tres conejos, se le administró 0.1 g. de la muestra en cada ojo y se lavó con 20 ml. de agua a los cuatro segundos. Al otro grupo de seis conejos se administró 0.1 g. de la muestra en cada ojo y no se lavó posteriormente. Se realizaron lecturas durante 7 días.

**CLASIFICACIÓN OBTENIDA:**

| | |
|---|---|
| Grupo ojos lavados | No Irritante |
| Grupo ojos sin lavar | No Irritante |

**Cuadro de resultados:**

| Grupo: Ojos Lavados | | | 1h | 24 hs | 48 hs | 72 hs | 96 hs | 7 Días |
|---|---|---|---|---|---|---|---|---|
| CONEJO Nro. | LESIONES OCULARES | | 08/09/2014 | 09/09/2014 | 10/09/2014 | 11/09/2014 | 12/09/2014 | 15/09/2014 |
| 1 | córnea | opacidad | 0 | 0 | 0 | 0 | 0 | 0 |
| | | área | 0 | 0 | 0 | 0 | 0 | 0 |
| | iris | | 0 | 0 | 0 | 0 | 0 | 0 |
| | conjuntiva | enrojecimiento | 0 | 0 | 0 | 0 | 0 | 0 |
| | | edema | 0 | 0 | 0 | 0 | 0 | 0 |
| | | secreción | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | córnea | opacidad | 0 | 0 | 0 | 0 | 0 | 0 |
| | | área | 0 | 0 | 0 | 0 | 0 | 0 |
| | iris | | 0 | 0 | 0 | 0 | 0 | 0 |
| | conjuntiva | enrojecimiento | 0 | 0 | 0 | 0 | 0 | 0 |
| | | edema | 0 | 0 | 0 | 0 | 0 | 0 |
| | | secreción | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | córnea | opacidad | 0 | 0 | 0 | 0 | 0 | 0 |
| | | área | 0 | 0 | 0 | 0 | 0 | 0 |
| | iris | | 0 | 0 | 0 | 0 | 0 | 0 |
| | conjuntiva | enrojecimiento | 0 | 0 | 0 | 0 | 0 | 0 |
| | | edema | 0 | 0 | 0 | 0 | 0 | 0 |
| | | secreción | 0 | 0 | 0 | 0 | 0 | 0 |
| Totales | Total Cornea | | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 |
| | Total Iris | | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 |
| | Total Conjuntiva | | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 |
| Scores diarios promedios | | | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 | 0,0 |

# Study on primary dermal irritability:

EDYAFE
Tecnología y experiencia a su servicio

Laboratorios Biomic S.R.L
Valentín Virasoro 1073
(1405) Buenos Aires - Argentina
Tel/Fax: 4982-0329 (Línea rotativa)
e-mail: info@biomic.com.ar
website: www.biomic.com.ar

Sistema de Gestión de Calidad ISO 9001:2008 acreditado por el Bureau Veritas con acreditcions que lo respaldan

(Para corroborar la autenticidad del presente ingrese esta clave en nuestra página Web: sZ6juytcKE )

PROTOCOLO Nº **83060** hoja 1 de 1

Buenos Aires, jueves, 11 de septiembre de 2014
Remitente: Brix SRL
Muestra declarada BRIX 3000 PLUS

Identificación: Lote: 20140724 100 Vto: 24/07/2016
Solicita: Test de Irritación Primaria Dérmica (Cod.: 437)
Fecha Inicio de Ensayo: 08/09/2014 Fecha de terminación del ensayo: 11/09/2014
Nota: El muestreo fue realizado por el remitente.

**MÉTODO:**

De acuerdo al método de H.J. Draize, se usaron 6 conejos albinos, machos o hembras, de peso corpóreo de 2 a 3 kg. 24 horas antes del ensayo se rasura una superficie en el lomo de 2,5 x 2,5 cm. Se aplica 0,5 g de la muestra el primer día del ensayo a cada conejo en la zona rasurada. 24 hs. más tarde se limpia la zona y se procede a las lecturas de las lesiones dérmicas. A las 72 horas de iniciado el ensayo se realiza una nueva lectura.
Los animales fueron mantenidos durante todo el período de prueba en jaula individuales a temperatura de 22º C + / - 2º C y humedad relativa entre 30 % y 70 %.

**La muestra fue aplicada:** sin parche oclusivo

| LESIONES DÉRMICAS EN CONEJOS | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fecha de lectura | Conejo 1 | | Conejo 2 | | Conejo 3 | | Conejo 4 | | Conejo 5 | | Conejo 6 | |
| | A | B | A | B | A | B | A | B | A | B | A | B |
| 09/09/2014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11/09/2014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| EVALUACIÓN DE LAS LESIONES | |
|---|---|
| **A - FORMACIÓN DE ERITEMAS Y ESCARAS** | **B - FORMACIÓN DE EDEMAS** |
| 0: ausencia de eritema | 0: ausencia de edema |
| 1: muy ligero eritema | 1: muy ligero edema |
| 2: bien definido eritema | 2: bien definido edema |
| 3: moderado eritema | 3: moderado edema |
| 4: severo eritema | 4: severo edema |

**Observaciones:**

Sin observaciones.

| CLASIFICACIÓN | |
|---|---|
| No irritante | 0 |
| Pract. No irritante | 0.1 - 0.99 |
| Minim. Irritante | 1.0 - 1.99 |
| Moder. Irritante | 2.0 - 5.99 |
| Sever. Irritante | 6.0 - 8 |

| CLASIFICACIÓN OBTENIDA | |
|---|---|
| 0,00 | No irritante |

Dr. David Sapoznikow
M.N. 1182-b

Este protocolo fue validado electronicamente. Es copia fiel del original alojado en servidores.

# Safety and effectiveness.

## *AMFE Table (Risk Management Report).*

| # | Failure mode | Failure effect | Cause of failure | Acceptability F | S | D | NPR | Action reduction / risk prevention | Acceptability F | S | D | NPR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Very thick product, not output from the siringe. | 1.1 Low wetting and penetration. | 1.1.1. High viscosity. Bad formulation | 3 | 1 | 3 | 9 | Heavy control labels<br>Control Production Order<br>Batch control raw material<br>Process Controls<br>Final product testing | 1 | 1 | 1 | 1 |
| 2. | Removal of carious tissue does not occur. | 2.1 Low or no enzyme activity. | 2.1.1 pH out of range | 3 | 1 | 3 | 9 | Process Controls<br>Control pH | 1 | 1 | 1 | 1 |
| | | | 2.1.2 Product expired | 3 | 1 | 2 | 6 | PB-026 Products procedure Defeated Includes expiration date on the container and the legend "Do not use after the expiration date". | 1 | 1 | 1 | 1 |
| | | | 2.1.3 The product was exposed to high temperatures | 3 | 1 | 3 | 9 | The package includes the conditions of the product. | 1 | 1 | 1 | 1 |
| 3. | The appearance of the gel is out of specification. | 3.1. Non crystalline gel. | 3.1.1. Bad formulation. | 3 | 1 | 3 | 9 | Heavy control labels,<br>Control of production order (step by step).<br>Visual Process Controls. | 1 | 1 | 1 | 1 |
| | | | 6.1.2. Contaminant siringes material. | 3 | 1 | 3 | 9 | The siringes material is selected to withstand storage conditions. | 1 | 1 | 1 | 1 |
| 4. | It is placed with painful symptoms or fistulas present. | 4.1. Does not cause the desired effect. | 4.1.1. Professional untrained / unknown product | 3 | 1 | 3 | 9 | It is planned conferences and training courses for dentists. | 1 | 1 | 1 | 1 |
| 5. | Dry or crusty product. | 5.1. Moisture loss. | 5.1.1. Syringe not closed or closed incorrectly. | 3 | 1 | 3 | 9 | PB-034 Use of equipment, tuning equipment online.<br>Final inspection. | 1 | 1 | 1 | 1 |
| 6. | Spatter product to the ocular región. | 6.1 Ocular burning. | 6.1.1. Problems in handling. | 3 | 1 | 3 | 9 | Eye irritation tests were performed with results: No irritant | 1 | 1 | 1 | 1 |

# Safety and effectiveness. *AMFE Table*

## Risk management report conclusion:

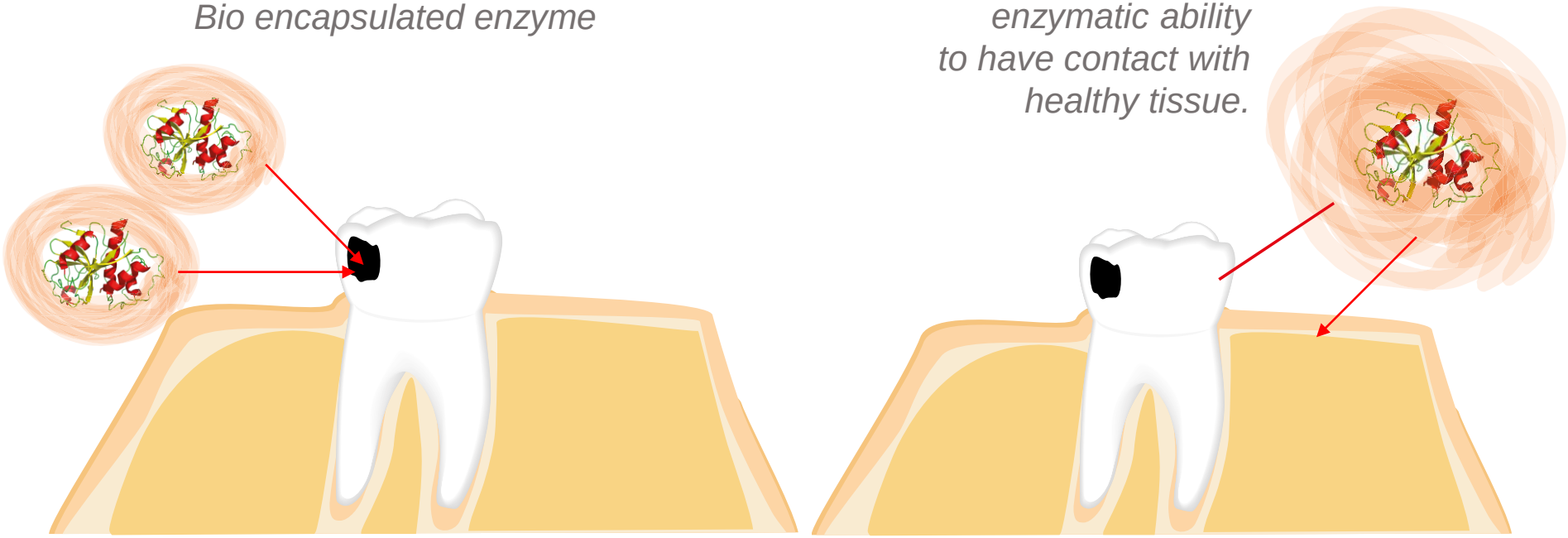
According to this assessment, the risks observed BRIX 3000 are within the Alarc and Fair area, so we conclude that it is safe under the conditions of use raised by BRIX S.R.L. product, ensuring the quality of the product offered.

# Selectivity

Papain acts only in the injured tissue due to the absence of a plasma antiprotease, the α1-anti-trypsin, which prevents its proteolytic action on normal tissues considered. The α1-anti-trypsin inhibits protein digestion. A present time, papain contribute to degradation and elimination of the "layer" fibrin formed by the process of caries.

*Bio encapsulated enzyme*

*The enzyme loses its enzymatic ability to have contact with healthy tissue.*



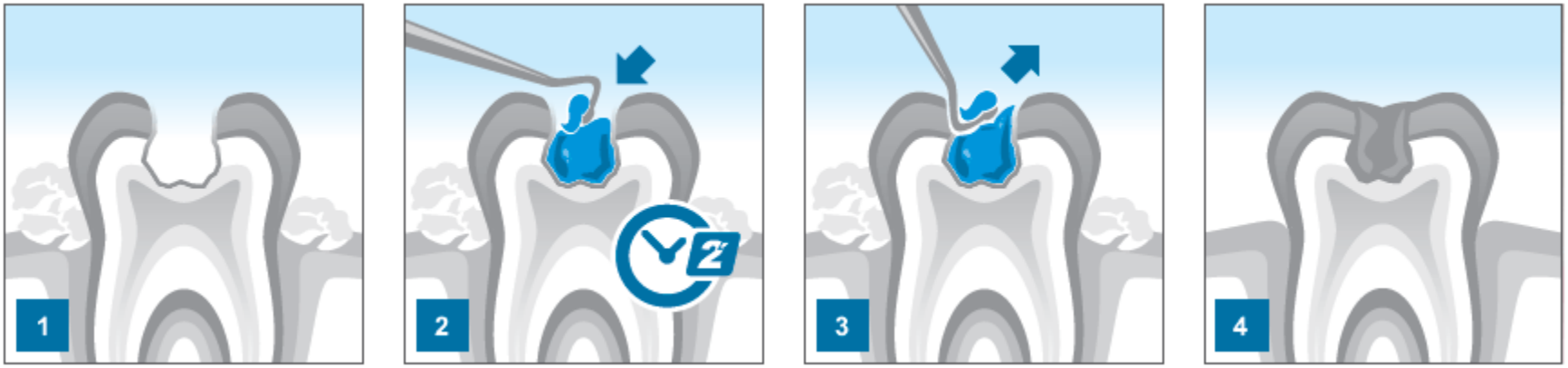
# Advantages

- Applicable in all age decreases the application of local anesthetics and instruments Rotarian.
- Not sacrifice healthy tissue and selective action exerted necrotic tissue is inactivated by α1-anti-trypsin present in dentin remineralizing possibility.
- No refrigeration needed.
- Community use in massive odontology (without use of large or rotary electric instruments or compressors).
- Reduces the risk of pulp exposures.
- Tranquility patient, dentist companions and the absence of stress.
- After removal of carious tissue, the cavity presents a roughened surface that facilitates adhesion of materials.

# Advantages

- Selective: Only on necrotic dentin.
- Atraumatic: Removal with handpiece, without pressure, low or no use of rotary instrument.
- Minimally Invasive: No vibrations. No noise from the turbine. Without application of anesthetics. Without pain.
- Integral: Addresses not only the sealing of the piece but also deals with pre-existing phobia or the patient.

# Product application

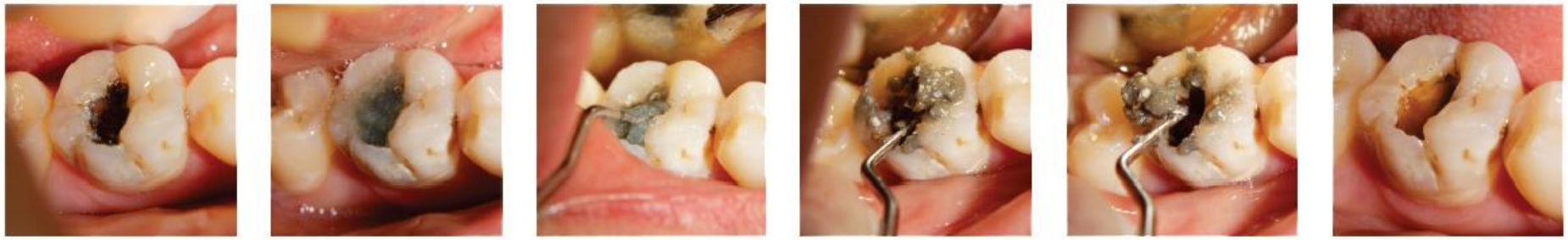



1. Relative isolation of target tooth with cotton ball.
2. Apply BRIX3000 with a blunt spoon allowing the chemistry to work for 2 minutes.
3. Remove material with blunt spoon with pendulum movement and without pressure.
   - If necessary, repeat the procedure to get to healthy dentin
   - Confirm the presence of healthy dentin with caries explorer and detector.

4. If necessary, restore the pulp. Apply obturating material immediately.

# Clinical Cases

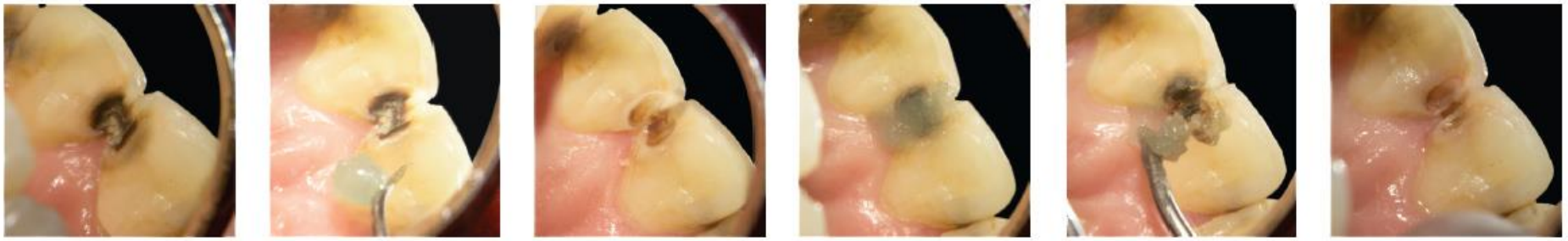
# Clinical Case 1



Female Patient, 23 . Occlusal Cavity. Piece 46.

No anesthetic or turbine are used.

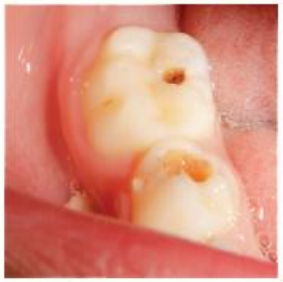
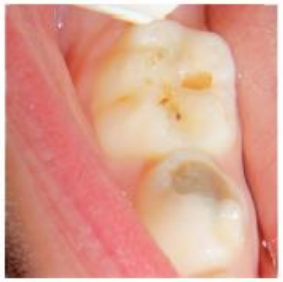
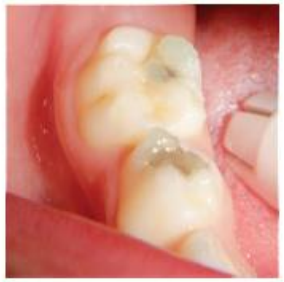
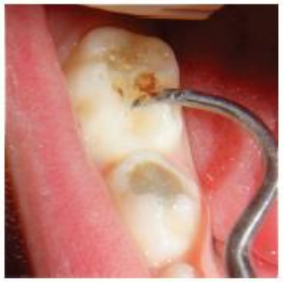
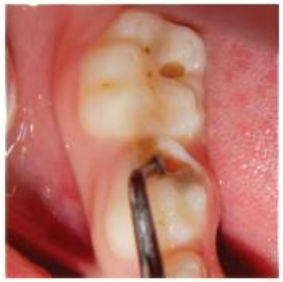
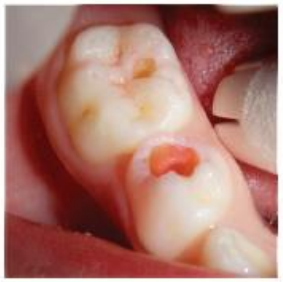
# Clinical Case 2



Female Patient, 40 . MD Proximal Cavities . Pieces 11 and 21. Simultaneous Treatment.

No anesthetic or turbine are used.

# Clinical Case 3

Male patient, 5 years old. Occlusal Cavities . Pieces 75 and 74 . Simultaneous Treatment.

No anesthetic or turbine are used.

# Clinical stadistics

Actually, more than 70.000 dental caries were removed by dentist professionals in Argentina and more than 5.000, in Colombia, without registering secundary effects of any kind in all patients treated.

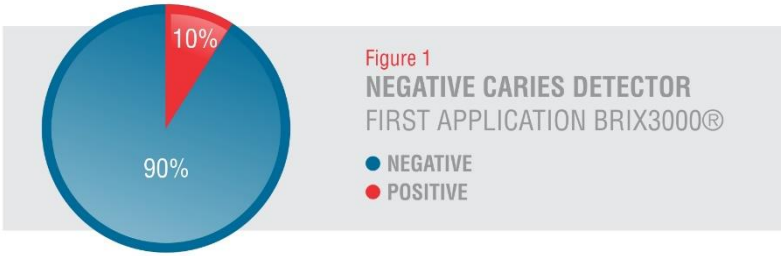
None of the patients have shown inflammatory reactions in the tissues surrounding the treatment area.

# Clinical stadistics

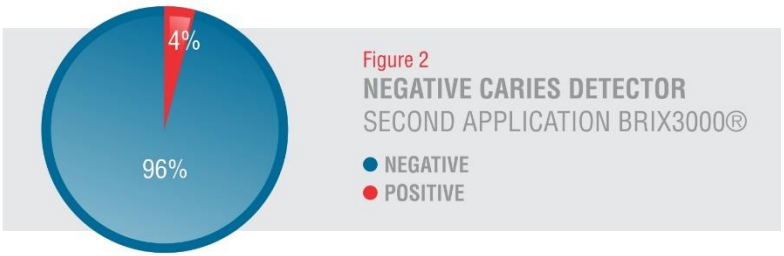
As regards BRIX 3000®'s exposure to caries detector, it has shown high effectiveness in its first application (90% negative) and in its second application (negative 96%) fig 1 and 2.

The technique does not produce volatile residues.
Total operating time: The enzymatic technique took 16 minutes on average with a 2.5-minute standard deviation. While in the rotary technique it took 34 minutes with a 4- minute deviation.
Patience preference: High acceptance of the enzymatic technique, preference by comparison

1. NEGATIVE CARIES DETECTOR
**FIRST APPLICATION**




2. NEGATIVE CARIES DETECTOR
**SECOND APPLICATION**



# Clinical stadistics

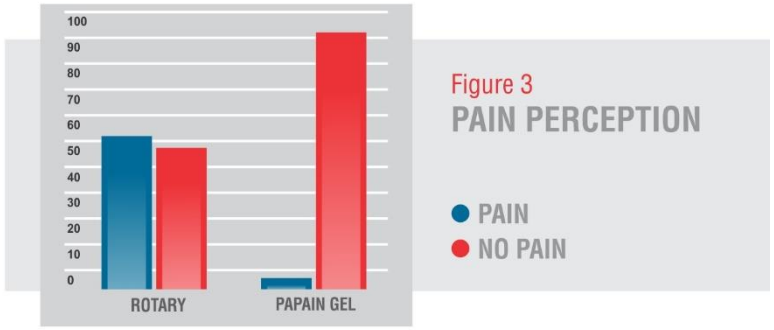
As regards pain degree, 93% of the patients have not suffered from pain. Fig 3.

BRIX3000® can remain in the oral cavity before starting drying for enough time.

Subjective efficacy which has been measured by the operator resulted in the following: all the professionals who have taken part in this have preferred BRIX3000® as their working material to traditional caries treatment.

Pre and post treatment difference of the cavity size: BRIX3000® has shown high conservation of biological material in comparison to conventional techniques. Fig 4.

### 3. PAIN PERCEPTION




### 4. PRE AND POST OPERATIVE CAVITY SIZE