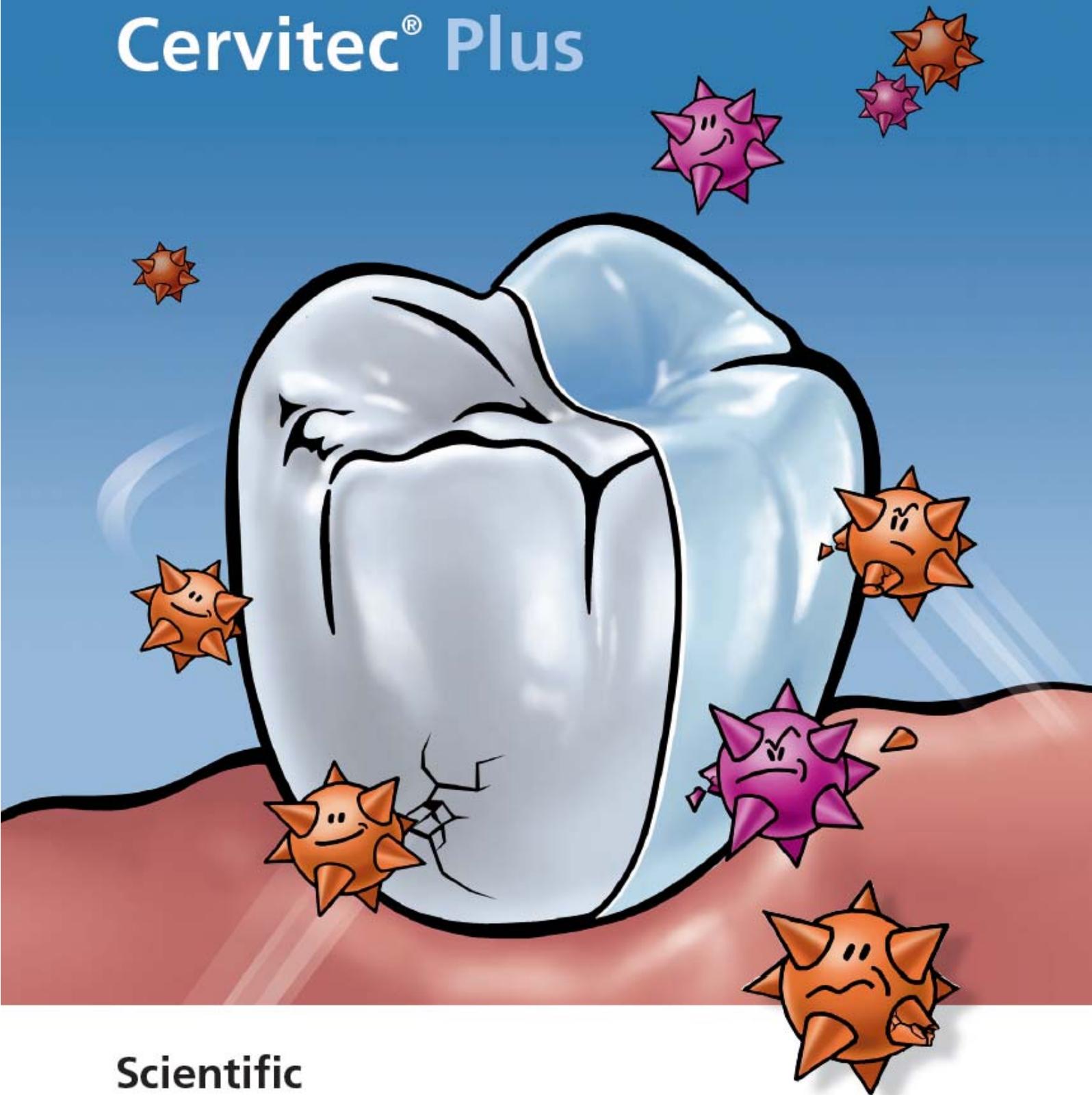


Cervitec® Plus



**Scientific
documentation**

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1. Introduction

Cervitec Plus is a further development of Cervitec, the chlorhexidine-containing protective varnish, which has been successfully used since 1993.

Indications include

- protection of exposed root surfaces
- treatment of hypersensitive cervicals
- reduction of bacterial activity on tooth surfaces

Cervitec Plus contains an innovative varnish component, which is responsible for the material's improved adhesion compared to the original Cervitec and ensures a high degree of desensitization. The varnish component is dissolved in ethanol/water, which reduces the material's susceptibility to moisture during application. As the organic solvent ethyl acetate, which is generally perceived as unpleasant, has been replaced with a neutral ethanol-water mixture, the product is more acceptable even for sensitive patients.

The tried-and-tested composition, which includes 1% chlorhexidine diacetate and 1% thymol as active antimicrobial ingredients, has been maintained. Once the varnish has been applied and dried, it contains approximately 10% of chlorhexidine and 10% of thymol.



2. Composition

Composition of the sales article (in weight %):

Function	Component	(in weight %)
Solvent	Ethanol, water	90
Excipients	Vinyl acetate co-polymer and acrylate co-polymer	8
Active ingredient	Thymol	1
Active ingredient	Chlorhexidine diacetate	1

Composition of the dried Cervitec Plus varnish (in weight %):

Component	(in weight %)
Vinyl acetate co-polymer and acrylate co-polymer	~ 80
Thymol	~ 10
Chlorhexidine diacetate	~ 10

pH value	6.5 - 7
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3. Treatment of hypersensitive cervicals

Many patients are affected by hypersensitive cervicals. Even though hypersensitive cervicals are not a pathological condition in the narrower sense, they cause an inconvenience to patients and may have a substantial adverse effect on their quality of life and often lead to a deterioration in oral hygiene.

Usually, open dentinal tubules are the underlying cause for tooth hypersensitivity. Dentinal tubules may be exposed due to iatrogenic processes (tooth preparation in the dental practice) or the loss of the protective enamel sheath / the smear layer on the tooth surface (e.g. because of excessive tooth brushing). The hydrodynamic theory of tooth sensitivity is widely accepted today to explain the mechanism involved in hypersensitive teeth. Assumptions of the hydrodynamic theory conclude that the sensory nerves of the tooth are activated due to the quick bi-directional fluid flow caused by certain stimuli within the dentinal tubules. Stimuli, e.g. temperature changes or osmotic activity, elicit pressure changes within the dentin, which lead to an excitation of certain nerves in the tooth. *In vivo* studies have revealed that the response of the pulp nerves is related to the pressure exerted and thus to the rate of fluid movement [1].

Consequently, there are two approaches to treating hypersensitivity: (a) sealing the dentinal tubules to prevent movement of fluid, or (b) inhibiting the neuronal transmission of the stimuli. The first mechanism is employed in the large majority of currently available products for the treatment of hypersensitive teeth.

Cervitec / Cervitec Plus also rely on the sealing of open dentinal tubules to reduce hypersensitivity. The desensitizing effect of these products has been tested and confirmed in laboratory tests and clinical trials [2; 3].

3.1 *In vitro* investigations

3.1.1 *Reduction in dentin permeability*

The efficacy of dentin sealing can be evaluated *in vitro* with the dentin permeability test according to Pashley. In this test, the fluid movement across sealed and unsealed dentin discs is measured. The reduction in dentin permeability after the application of Cervitec Plus in comparison with Cervitec and Gluma was measured in human dentin. Teeth with a smear layer were used as a control. The presence of the smear layer is a natural condition in teeth without tooth sensitivity problems. In this investigation, Cervitec Plus showed the highest reduction in permeability on average and achieved a sealing efficacy comparable to that of the smear layer (see Figure 1).

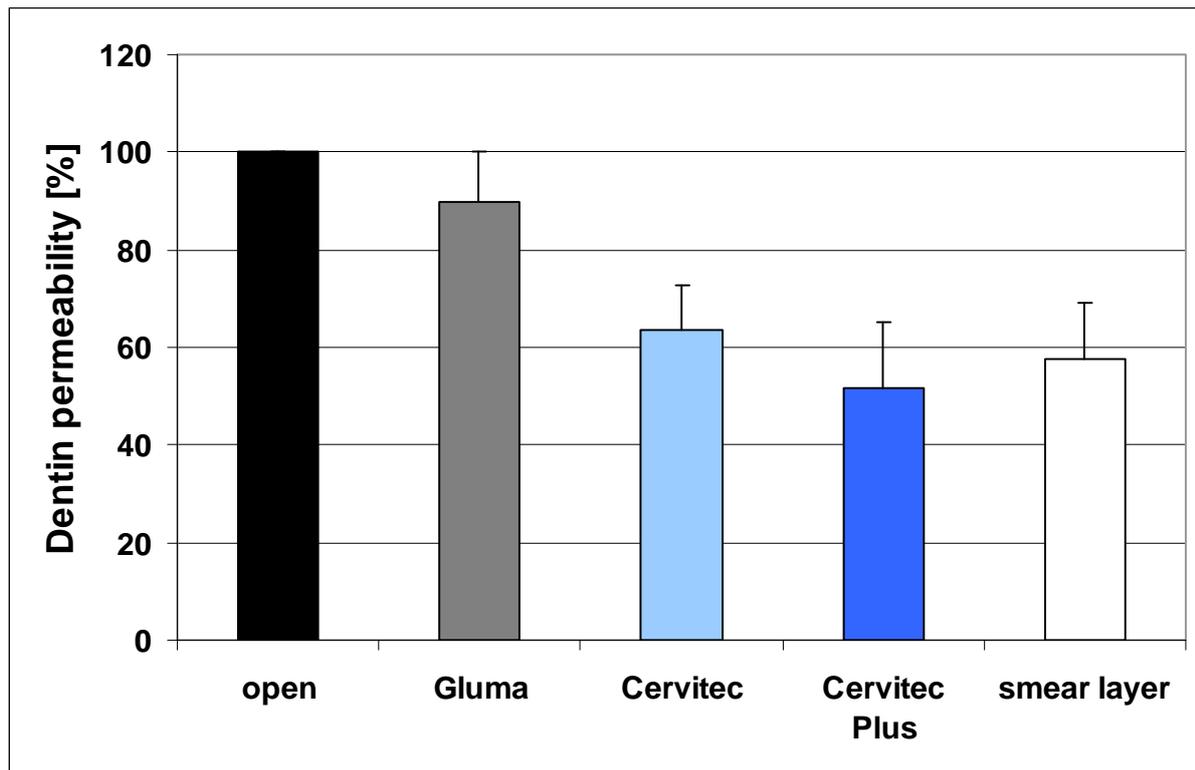


Figure 1: Dentin permeability after treatment with different materials. The fluid movement across human dentin discs was measured in samples that had been treated with various desensitizers (Gluma, Cervitec, Cervitec Plus) and in untreated samples (open tubules). Dentin with a natural smear layer was employed as positive control. Cervitec and Cervitec Plus achieved a similar reduction in dentin permeability as the natural smear layer.

Study: Prof Dr Grégoire, Toulouse, France

3.2 Clinical studies

3.2.1 Desensitizing effect in patients with exposed root dentin surfaces

A three-armed, randomized placebo-controlled clinical study investigated the efficacy of Cervitec und Cervitec Plus as desensitizing agent in patients with exposed root dentin surfaces. Each of the three groups (Cervitec Plus, Cervitec, placebo) contained 40 patients. Each formulation was applied once. Hypersensitivity was evaluated at the beginning of the study, after one day, one week, one month and three months; tooth sensitivity was triggered using cold water or blown air and the pain experienced was rated on a scale from 0 to 4.

The results (see Figure 2) show that Cervitec Plus and Cervitec significantly reduced the intensity of the pain, while no clinically meaningful improvement was noticed in the placebo group. The effect of both varnishes was already perceptible one day after their application and a significant improvement was observed after seven days. The favourable results were confirmed after four weeks. The effect of both varnishes remained stable without noticeable difference up to this point of time. After three months, the protective effect of Cervitec Plus remained unchanged, while the effect of Cervitec started to decrease.

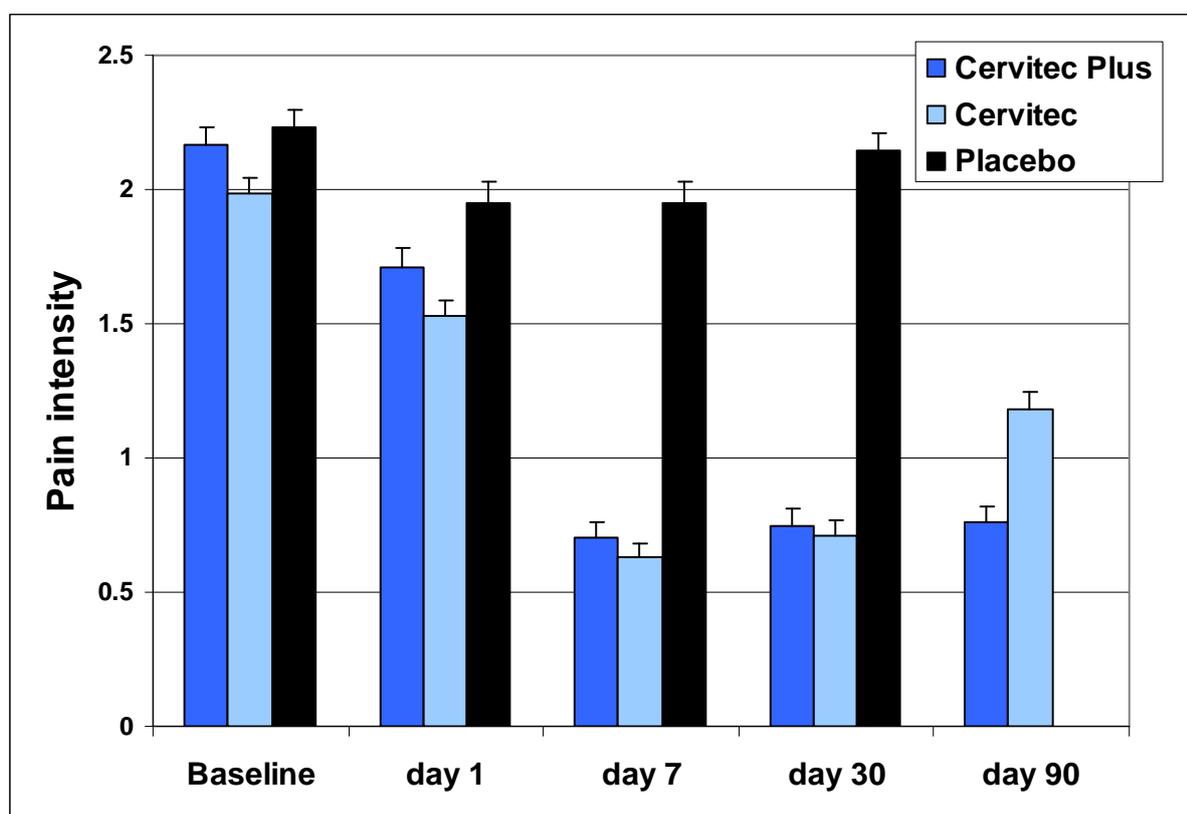


Figure 2: Reduction in the intensity of pain after treatment with Cervitec / Cervitec Plus. The intensity of pain was recorded for 40 patients, who received a one-time application of either Cervitec, Cervitec Plus or a placebo. The chart above shows the mean values with the standard error margin. Both Cervitec varnishes resulted in a quick and long-lasting reduction in the intensity of pain.

Study: Dr Dirk Ziebolz and Prof Dr Rainer Mausberg, University of Göttingen, Germany

4. Reduction of antibacterial activity and caries prevention

Over the last few centuries, chlorhexidine has evolved into the gold standard among the antimicrobial substances used in dentistry. It has been demonstrated to be effective against a wide spectrum of pathogenic organisms. In high concentrations (100 ppm), chlorhexidine is capable of destroying the cell membranes of bacteria and thus has a bactericidal effect. A bacteriostatic effect is achieved at a concentration of only 0.11 ppm chlorhexidine. The cariogenic *S. mutans* is particularly sensitive to chlorhexidine. The particular effectiveness of chlorhexidine compared to other substances is certainly related to its high substantivity. As a result, it deposits on oral surfaces, creating slow-release reservoirs. The substantivity of chlorhexidine is attributable to interactions between chlorhexidine, which carries a positive charge, and structures, which carry a negative charge, such as proteins, glycoproteins of the saliva, plaque and the enamel hydroxyapatite. The use of a varnish system decisively promotes depot formation. Long-term therapy with chlorhexidine mouth rinses and gels can lead to discoloration of teeth, the mucous membrane, tongue and composite restorations. These undesirable side effects can be avoided by using a chlorhexidine-containing varnish.

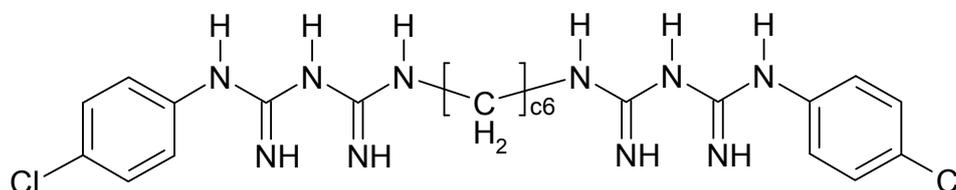


Figure 3: Chlorhexidine. The structural formula shows, among others, a large number of NH-groups, which are responsible for the positive charge of the molecule.

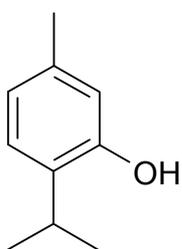


Figure 4: Thymol

Cervitec Plus contains thymol in addition to the antimicrobial substance chlorhexidine. Thymol is found in essential oil of thyme and is extracted from thyme (*Thymus vulgaris*). Thymol belongs to the class of phenol compounds and, similar to chlorhexidine, has an antimicrobial effect and is also effective against (yeast) fungus ("fungistatic"). Its efficacy is based on the denaturation of proteins and the destruction of cell membranes.

4.1 In vitro investigations

4.1.1 Inhibition zone assay

To evaluate their antimicrobial effect, Cervitec Plus and Cervitec were applied to Tetric Ceram test specimens and placed on strain-specific culture media, which had previously been inoculated with mutans streptococci. The Cervitec and Cervitec Plus specimens showed contact inhibition zones in all cases, i.e. the growth of bacteria was inhibited. On average, Cervitec Plus demonstrated larger inhibition zone sizes. However, no significant difference between Cervitec (n=14) and Cervitec Plus (n=11) was found (Student's t-test p=0.18).

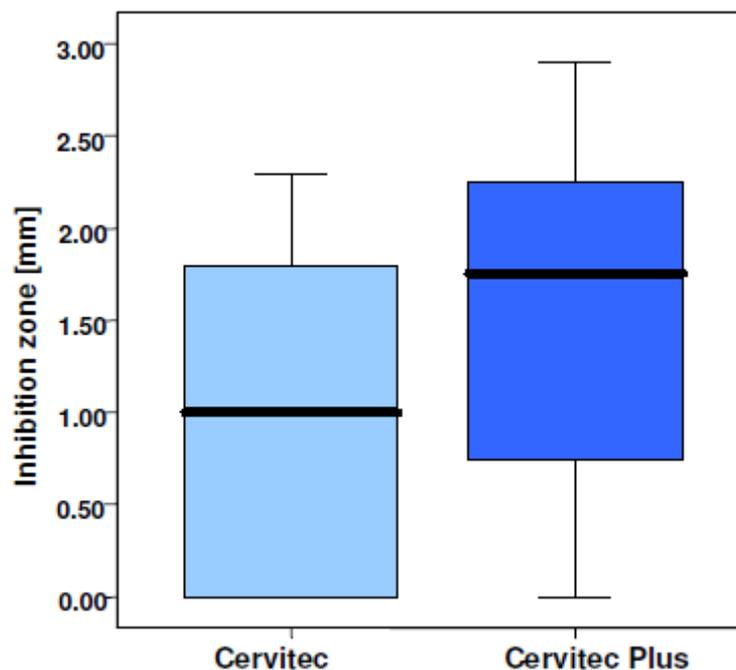


Figure 5: Antibacterial effect of Cervitec and Cervitec Plus. Cervitec and Cervitec Plus were applied to composite test samples, which were then placed on agar plates, which had been inoculated with mutans streptococci. The inhibition zone size is an indication of the strength of the antibacterial effect. Cervitec and Cervitec Plus inhibited bacterial growth similarly well.

Study: Ivoclar Vivadent, R&D, Schaan, Liechtenstein

Similar inhibition zone assays were carried out for other relevant oral microorganisms. The contact inhibiting effect was visually determined.

Table 1: Antibacterial effect of Cervitec and Cervitec Plus. Cervitec and Cervitec Plus were applied to composite test specimens and subsequently placed on agar plates, which had previously been inoculated with various microorganisms. "Yes" means that inhibition zones were detected.

Microorganism	Cervitec	Cervitec Plus
<i>Streptococcus mutans</i> DSM20523	yes	yes
<i>Streptococcus sobrinus</i> DSM20742	yes	yes
<i>Actinomyces naeslundii</i> DSM43013	yes	yes
<i>Candida albicans</i> DSM1386	yes	yes

Study: Ivoclar Vivadent, R&D, Schaan, Liechtenstein

4.1.2 Antimicrobial effect on root canal surfaces

Thneibat A, Fontana M, Cochran MA, Gonzalez-Cabezas C, Moore BK, Matis BA, Lund MR (2008). Anticariogenic and antibacterial properties of a copper varnish using an *in vitro* microbial caries model.

This *in vitro* study investigated the antibacterial effect of various varnishes (“Copper Seal” – an experimental copper-containing varnish with and without removal 24 h after application, Cervitec and an untreated control group) in a microbial caries model using 56 human root specimens. After five days, the bacterial count in the resultant plaque and the extent of the lesions were assessed by means of confocal laser scanning microscopy. The bacterial count was not significantly different in the individual groups. The carious lesions, however, were significantly larger in the control group and the copper varnish group with varnish removal after 24 h than in the copper varnish group without removal and the Cervitec group. It was therefore assumed that Copper Seal and Cervitec may act against caries on root canal surfaces [4].

4.2 Clinical studies on caries-preventive effect

Chlorhexidine is an efficacious substance in the prevention of caries because of its antimicrobial effect. A reduction in cariogenic microorganisms in the oral cavity leads to a decrease in the production of acids, which attack the tooth structure. As a result, the development of caries can be effectively prevented. A review article compares the efficacy of various chlorhexidine-containing varnishes in the prevention of caries. A summary of the results obtained in several studies has revealed that the preventive effect of Cervitec is superior to that of the other chlorhexidine-containing varnishes (see Figure 6) – in four of five studies, a statistically significant caries inhibition effect was observed after the application of Cervitec [5].

Varnish	Application frequency	Localization of caries	Source
Cervitec	3-4 months	D	[6]
Cervitec	3 months	E	[7]
Cervitec	3 months	D	[8]
Cervitec	3 months	E + D	[9]
EC40	3-9 months	D	[10]
EC40	6 months	D	[11]
EC40	6 months	E + D	[11]
Chlorzoin	3-6 months	D	[12]
Chlorzoin	3-6 months	E + D	[12]
EC40	6 months	E + D	[13]
Cervitec	3 months	D	[14]

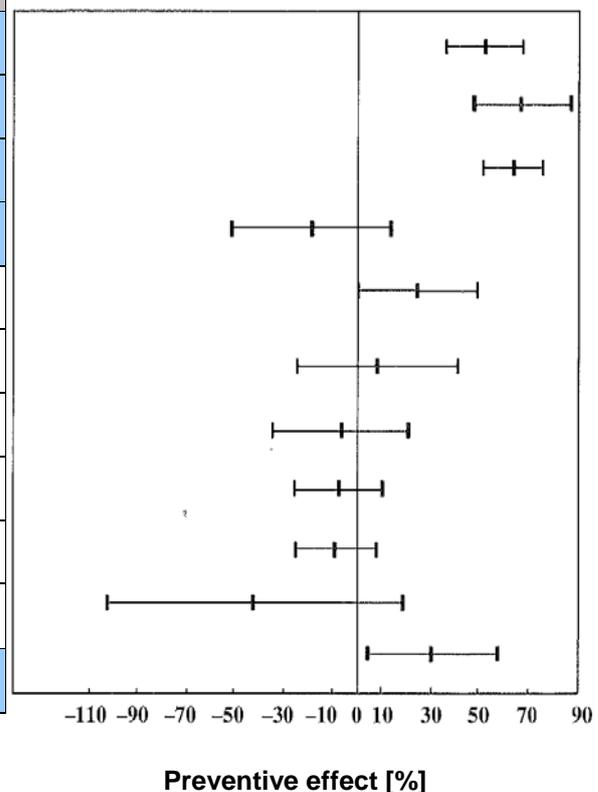


Figure 6: Caries prevention with CHX varnishes. The preventive effect (“preventive fraction”) of CHX varnishes was assessed in a number of studies. Cervitec demonstrated a statistically significant caries inhibiting effect in four of five studies. D: Dentin, E: Enamel.

A number of clinical studies on caries prevention in conjunction with Cervitec are described in detail below. These studies focus on specific risk parameters / patient groups / caries predilection sites.

4.2.1 Reduction in cariogenic microorganisms in vivo

Ersin NK, Eden E, Eronat N, Totu FI, Ates M (2008): Effectiveness of 2-year application of school-based chlorhexidine varnish, sodium fluoride gel, and dental health education programs in high-risk adolescents.

A two-year study conducted in Turkey among 149 11- to 13-year-old adolescents with a high caries risk compared the efficacy of three different preventive approaches: (a) Cervitec (application at baseline and then at three-month intervals; 50 patients), (b) sodium fluoride gel containing 4500 ppm fluoride (application at baseline and then at six-month intervals; 50 patients) and (c) oral health education (49 patients) including using a fluoride-containing tooth paste (1500 ppm) twice a day and a ten-minute session on oral health with each patient every three months. Caries growth, the plaque score and *S. mutans* count were evaluated. After twelve months, a statistically significant reduction in the *S. mutans* count was observed in the Cervitec group but not in the other groups. At the end of the study, all groups showed a similar plaque and caries growth index; however, the group that took part only in the oral health education programme, showed considerably higher *S. mutans* counts than the Cervitec or fluoride gel group [15].

Sköld-Larsson K, Borgström MK, Twetman S (2001): Effect of an antibacterial varnish on lactic acid production in plaque adjacent to fixed orthodontic appliances.

This study examined the effect of Cervitec on the number of mutans streptococci and their lactic acid production compared to a placebo varnish. Twenty-five adolescents with fixed orthodontic appliances were recruited into this double blind, split mouth study. Both varnishes were applied twice within the course of three days. Plaque samples were collected from the surroundings of the appliances after 3, 7 and 30 days. The mutans streptococci count and lactic acid production were determined. Cervitec was found to have significantly reduced the mutans streptococci counts after seven days. Lactic acid production was also reduced by approx. 20 % [16].

Petersson LG, Maki Y, Twetman S, Edwardsson S (1991): Mutans streptococci in saliva and interdental spaces after topical application of an antibacterial varnish in schoolchildren.

Petersson *et al.* investigated the concentrations of mutans streptococci in the saliva and interdental spaces in 33 15-year-old schoolchildren. Cervitec and a placebo were applied to the interdental spaces in the upper jaw at two-day intervals according to the split mouth method. The mutans streptococci counts in the saliva and the plaque were determined over a period of three months. Both the placebo and Cervitec applications resulted in an immediate reduction in bacteria. However, after 8, 30 and 90 days, only the test quadrant with Cervitec showed significantly lower counts. Thus, Cervitec is capable of inhibiting the recolonization of bacteria in interdental spaces for a sustained period of time [17].

4.2.2 Protection against demineralization

Bizhang M, Seemann R, Romhild G, Chun YH, Umland N, Lang H, Zimmer S (2007): Effect of a 40% chlorhexidine varnish on demineralization of dentin surfaces in situ.

An *in situ* study endeavoured to find out if chlorhexidine-containing varnishes (EC40 and Cervitec) are capable of protecting the dentin from demineralization. The test persons wore dentin samples made of extracted human teeth in the mouth. The volunteers were divided into three groups and a different varnish was administered in each group: EC40 (n=16), Cervitec (n=15) and, in the control group, ChemiFil fluoride and CHX free varnish (n=16). Surplus EC40 was removed eight minutes after application; the Cervitec varnish remained entirely on the test samples. The dentin samples were worn day and night for three weeks;

they were immersed in 10-% sucrose solution during mealtimes and rinsed with water but not cleaned with a brush. The degree of demineralization (depth of lesion and mineral loss) was measured by means of microradiography. The results revealed that both CHX varnishes were capable of significantly reducing the depth of lesion and mineral loss compared with the control, as can be seen in Figure 7 [18].

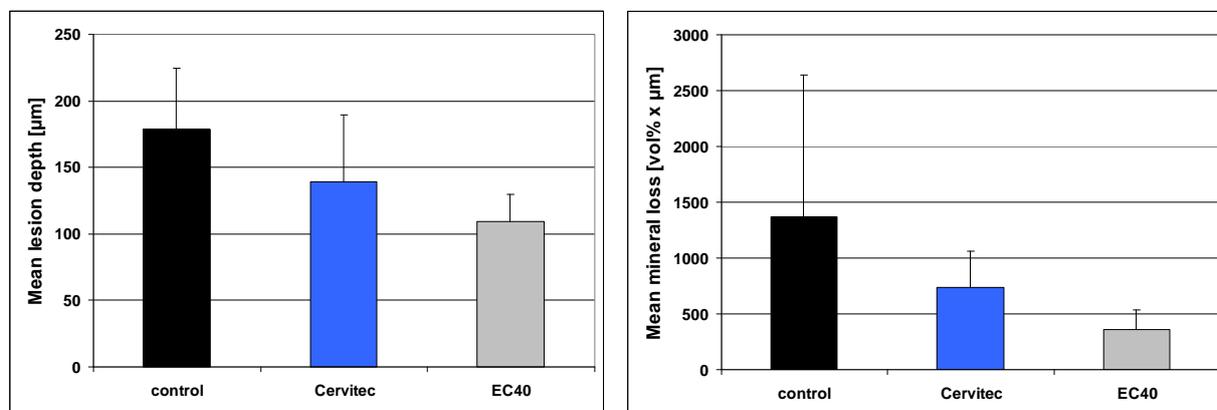


Figure 7: Protection against demineralization with CHX varnishes. CHX varnishes (Cervitec, EC40) and a placebo varnish (control) were applied to human dentin samples and carried in the mouth of volunteers for three weeks. The parameters for demineralization, i.e. lesion depth (on the right) and mineral loss (on the left), were determined by means of microradiography. The demineralization in both the Cervitec and EC40 group was statistically significantly lower than in the control group.

Adapted from Bizhang et al, 2007

4.2.3 Fissures

Today, almost 90% of all caries lesions in children are found in pits and fissures [19]. Since the enamel layer on the fissure floor is thinner and less well-mineralized, caries may progress into the dentin within a relatively short period of time. Fissure sealing is used as a preventive measure. If sealing is not possible, because appropriate moisture control cannot be achieved, the application of Cervitec Plus offers an effective alternative.

The caries-preventive effect of Cervitec in fissures was evidenced in a variety of clinical studies [6; 8; 14; 20-23]. Only a Brazilian study did not reveal a better effect for Cervitec than for the placebo varnish [24].

Sköld-Larsson K, Sollenius O, Petersson LG, Twetman S. (2009): Effect of topical applications of a novel chlorhexidine-thymol varnish formula on mutans streptococci and caries development in occlusal fissures of permanent molars.

In a double blind, split mouth study, Sköld-Larsson *et al.* compared the efficacy of the former formulation (Cervitec) with the new formulation (Cervitec Plus) of the CHX-thymol varnish. Fifty-eight adolescents aged between 12 and 17 with fixed orthodontic appliances were recruited into the study. Hundred and sixteen pairs of molars were randomly allocated to one of two groups; one group was treated with Cervitec and the other with Cervitec Plus. The varnishes were applied at baseline and then at six-week intervals until week 48. At the end-of the study, the mutans streptococci count was determined using the CRT bacteria test and the teeth were checked for occlusal decay using a DIAGNOdent device for laser-based caries diagnostics. Significantly reduced streptococci counts in the fissures were observed for both varnishes and these counts stayed at a low level over the entire length of the study. A slight, but statistically not significant tendency toward being more effective was observed in the new varnish formulation (see Figure 8) [20].

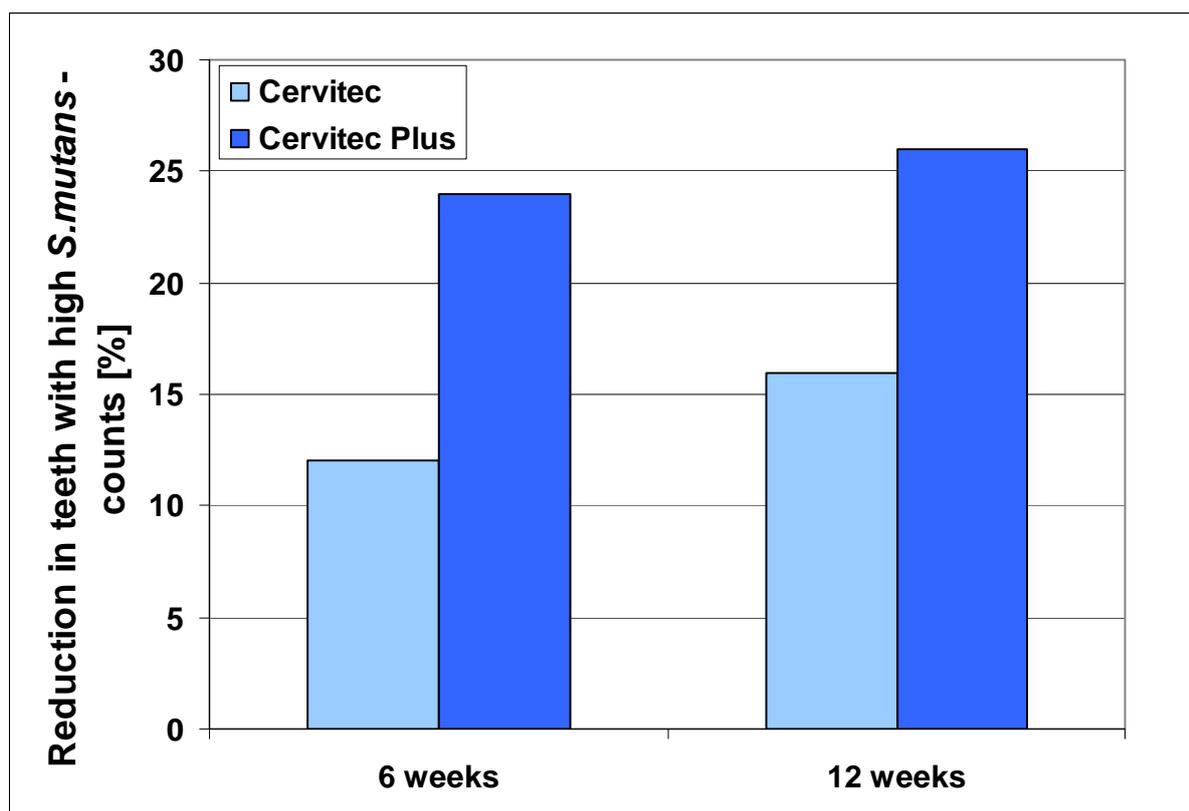


Figure 8: Reduction in teeth with high *S.mutans* counts. Cervitec or Cervitec Plus was applied to 116 pairs of molars in adolescents with fixed orthodontic appliances in a split mouth study. The mutans streptococci count in the fissures was determined using CRT bacteria. Both varnish versions lead to a significant reduction in the bacteria counts; however, Cervitec Plus showed a slight tendency toward being more effective.

Adapted from Sköld-Larsson et al, 2009

Sköld-Larsson K, Fornell AC, Lussi A, Twetman S (2004): Effect of topical applications of a chlorhexidine / thymol-containing varnish on fissure caries assessed by laser fluorescence.

This study also examined the development of fissure caries using a DIAGNOdent caries detector. Thirty-two children approximately aged 14 were treated with Cervitec or a placebo according to the split mouth method. They were re-examined at twelve-week recall intervals. The DIAGNOdent values, i.e. the frequency of fissure caries, increased by a significantly larger extent in the placebo group compared to the Cervitec group (see Figure 9) [23].

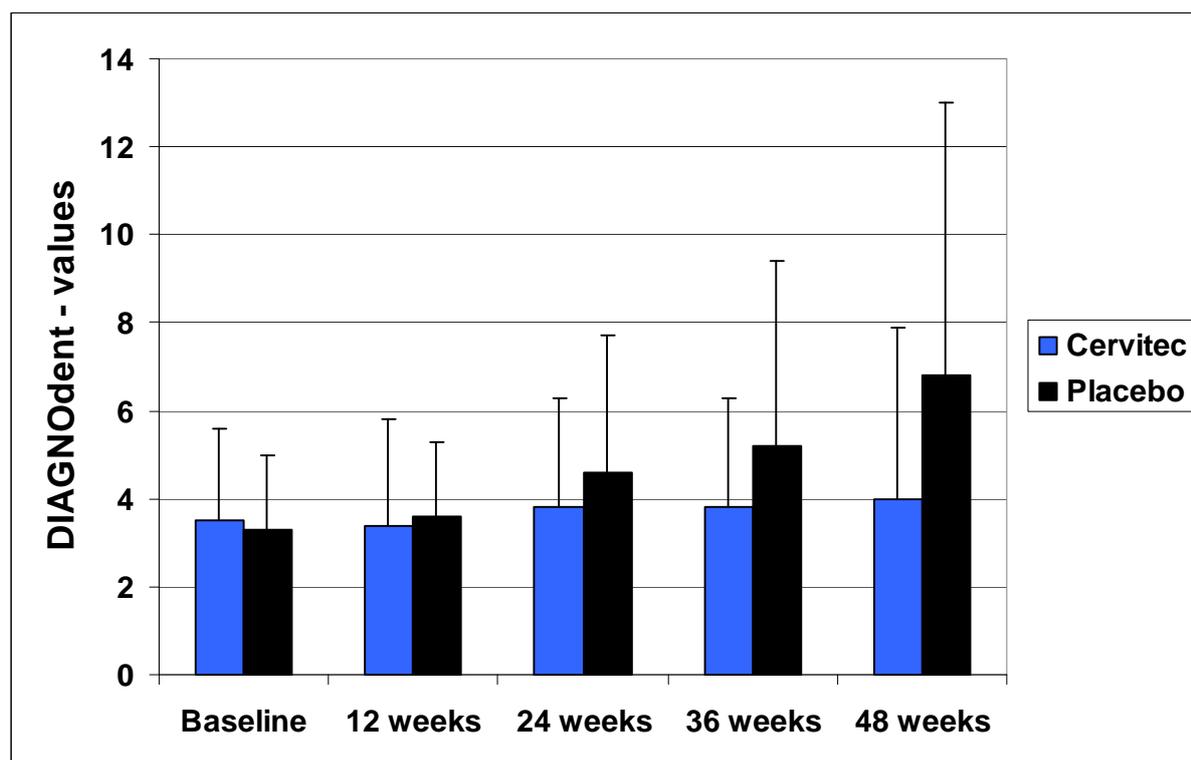


Figure 9: Protection against fissure caries with Cervitec. Cervitec or a placebo was applied to 14-year-old children in a split-mouth study. Recalls were conducted at twelve-week intervals. A laser fluorescent system for the detection of caries (Diagnodent) was employed to examine the molars for fissure caries. Fissure caries increased in the placebo group over the course of the study; Cervitec prevented the increase of caries.

Adapted from Sköld-Larsson et al, 2004

Baca P, Muñoz MJ, Junco P, Baca AP (2002): Effectiveness of chlorhexidine-thymol varnish for caries reduction in permanent first molars of 6-7-year-old children: 24-month clinical trial.

Cervitec appears to reduce the development of caries in permanent molars. This was shown in a two-year *in vivo* study involving 86 children in the test group and 95 children in the control group. The children were aged between six and seven years. If teeth cannot be sealed or if a general protective measure is desired for erupting molars, Cervitec presents a viable alternative for the prevention of caries [14].

Araujo A, Naspitz G, Chelotti A, Cai S (2002): Effect of Cervitec on mutans streptococci in plaque and on caries formation on occlusal fissures of erupting permanent molars.

Cervitec reduced mutans streptococci numbers in the plaque of erupting permanent molars and significantly decreased the caries susceptibility of these teeth. While the molars which were treated with Cervitec at three-month intervals remained free from caries, eight out of the 16 control teeth showed signs of incipient caries after two years [21].

Joharji RM, Adenubi JO (2001): Prevention of pit and fissure caries using antimicrobial varnish: 9 month clinical evaluation.

In this study, the increase in caries lesions in fissures correlated with the mutans streptococci count in the plaque of fissures. Cervitec significantly reduced the formation of fissure caries. These are the results of a nine-month study using a split mouth design and involving 94 seven- to eight-year olds and 86 12- to 14-year-olds [8].

Bratthall D, Serinirach R, Rapisuwon S, Kuratana M, Luangjarmekorn V, Luksila K (1995): A study into the prevention of fissure caries using an antimicrobial varnish.

Cervitec significantly reduced the development of fissure caries in applications that were carried out under field conditions. This was the outcome of a two-year study involving 211 seven-to-eight-year-olds and 212 12-to-13-year-olds. A split-mouth design was used in the study. The occlusal part of one molar was treated with Cervitec three times in the first year, while the opposing molar in the same arch served as a control [6].

4.2.4 Interdental spaces

Apart from fissure caries, approximal caries is the type of caries most frequently found in children and young adults. Incidence and extent of this type of caries are statistically correlated with the frequent consumption of sugar and high intraoral mutans streptococci counts.

The application of Cervitec and its effect on the bacterial burden and/or progression of caries was investigated in various studies [9; 25-33].

Heintze SD, Twetman S (2002): Interdental mutans streptococci suppression in vivo: a comparison of different chlorhexidine regimens in relation to restorative material.

Various chlorhexidine regimens were tested in 128 adults with high mutans streptococci counts over a period of three months. The following treatment approaches were tested: professional tooth cleaning with 1-% CHX gel (A), double application of Cervitec (B), single application of 40-% CHX varnish (C) or daily tooth brushing with a 1-% CHX gel for two weeks (D). Plaque samples were collected from the interdental spaces at baseline, after one week and after three months. Applied on intact enamel, amalgam and composite surfaces, all approaches lead to a reduction of the mutans streptococci count compared to the baseline. The reduction in mutans streptococci was statistically significant in groups B, C and D compared to group A [33].

Twetman S, Petersson L (1999): Interdental caries incidence and progression in relation to mutans streptococci suppression after chlorhexidine / thymol varnish treatments in schoolchildren.

In this two-year study, 110 children were treated with Cervitec according to the "intensive method" (three applications in the interdental spaces within two weeks). Sixty-three untreated children were used as a control. The mutans streptococci count was determined and the caries incidence and progression on proximal surfaces monitored for a period of two years. It was demonstrated that the reduction in caries incidence correlated with the reduction in MS counts ($p < 0.01$) [27].

Twetman S, Petersson L (1997): Effect of different chlorhexidine varnish regimens on mutans streptococci levels in interdental plaque and saliva.

This six-month study involving 88 schoolchildren showed that intensive treatment in which Cervitec was applied three times during the space of two weeks more effectively reduced the mutans streptococci levels than three applications distributed over a period of three months. The efficacy of these measures is best monitored with site-specific plaque samples, as a reduction of the bacteria in the susceptible interdental region is not always adequately shown in saliva samples [31].

4.2.5 Transmission from mother to child

In essence, early childhood caries (ECC) is a preventable disease. The main cause for ECC is the consumption of sweetened liquids – mainly sweetened teas, juices and all types of soft drinks from bottles and “sippy” cups, which infants are offered during day and night time hours. Parents of infants with significant risk factors should receive detailed dietary

counselling. Moreover, they should be motivated to use and be instructed in early oral hygiene procedures and informed about further preventive measures.

The use of Cervitec Plus can be a supportive measure. In various studies it could be shown that the application of Cervitec can have a preventive effect on the development and progression of early childhood caries. Two studies revealed that the preventive treatment of pregnant women reduced the transmission of mutans streptococci and caries incidence in infants.

Dubielecka M, Slotwinska SM (2005): Suppression of caries in mothers and caries risk in offspring.

The objective of this study was to investigate the caries-preventive effect of Cervitec in pregnant women and their babies. Cervitec was applied every six months in 97 women until their children were 36 months old (control group: 60 untreated women). The caries prevalence in the children of the mothers who were treated was significantly lower than in the children of the control group (see Figure 10) [34].

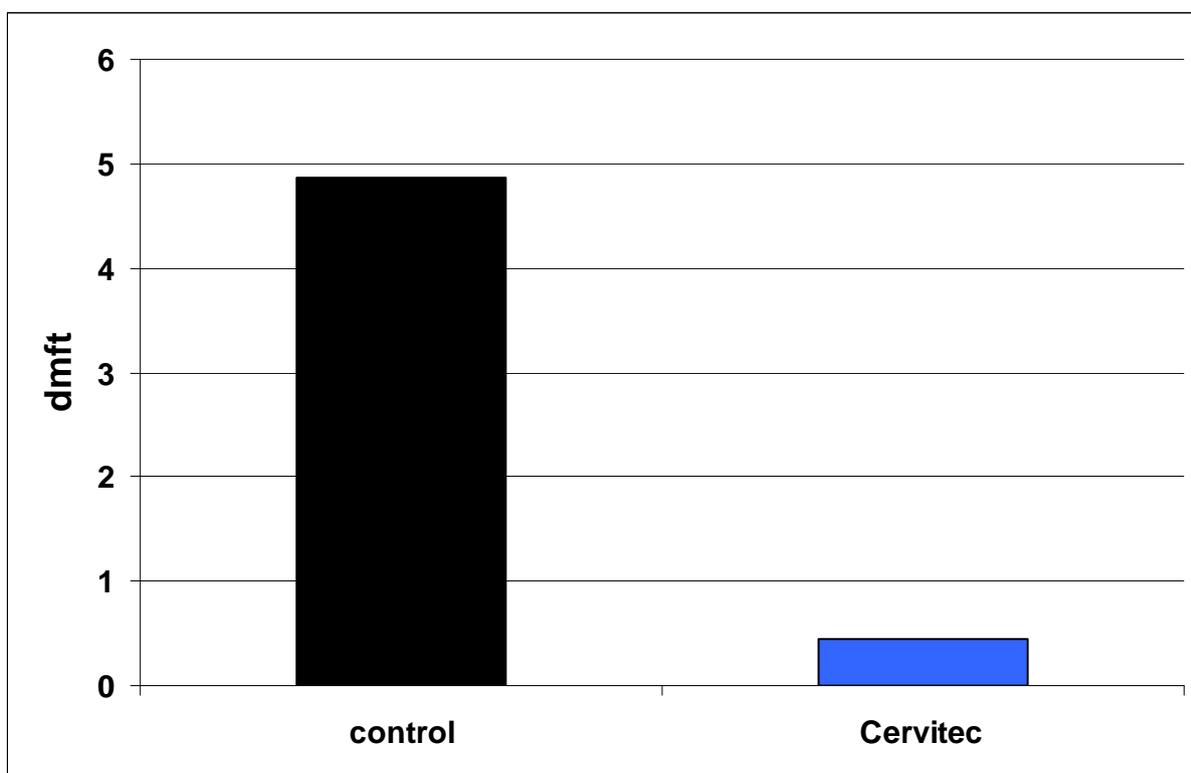


Figure 10: Reduction of early childhood caries by treating mothers with Cervitec. Cervitec was applied every six months in 97 women until their children were 36 months old (control group: 60 untreated women). The children of the mothers that were treated showed a significantly lower caries incidence (dmft) compared to the children of the control group.

Adapted from Dubielecka et al, 2005

Duskova J, Broukal Z, Kratky M (2000): Inhibition of the oral Streptococcus mutans transfer in the mother and child care: results in mothers and infants in the 3rd year of study.

Duskova *et al.* investigated the transfer of mutans streptococci to their children in the first two years of their life. The mothers treated with Cervitec demonstrated a lower increase in caries and plaque and a healthier gingiva compared to the control group. In addition, the prenatal and postnatal antimicrobial prophylaxis with Cervitec prevented the transmission of measurable amounts of mutans streptococci from mothers to their children [35].

4.2.6 Infants and primary teeth

Cervitec is not only suitable for mothers to reduce the risk of early childhood caries but has also proven to be effective when directly applied to children. The fast and easy handling of the Cervitec varnish represents an advantage, as the compliance of children is naturally limited.

Plotzitz B, Kneist S, Berger J, Hetzer G (2005): Efficacy of chlorhexidine varnish applications in prevention of early childhood caries.

In this study, the caries-preventive effect of Cervitec was evaluated in one-year-old children at high caries risk (> mutans streptococci level of 10^5 cfu/ml of saliva) and compared to an untreated control group. Cervitec was applied every three months for a period of one year and the caries status evaluated in the two-year olds. It was shown that, compared to the control group, caries was significantly reduced in this risk group due to the application of Cervitec ($p=0.02$ for dmfs). However, the study also revealed that poor dietary habits cannot be compensated by the use of Cervitec [36].

Baca B, Munoz M, M Bravo, P Junco, AP Baca (2004): Effectiveness of chlorhexidine-thymol varnish in preventing caries lesions in primary molars.

This study, which involved 181 six-to-seven-year-old school children, investigated the caries-preventive effect of Cervitec in comparison with a placebo in deciduous molars. Cervitec was applied every three months for a period of two years. It was shown that, after two years, the caries incidence could be reduced by 46% ($p=0.04$ for dfs) in children who were caries-free at baseline. No improvement of the situation could be achieved in children who already had caries [37].

4.2.7 Orthodontic patients

Good oral hygiene is even more important during orthodontic treatment than at any other time. When removable orthodontic appliances are worn, and in particular during orthodontic treatment with fixed orthodontic appliances, plaque is capable of adhering to the tooth surfaces more easily. If oral hygiene is insufficient, the increased accumulation of plaque and the microorganisms associated with plaque accretion may lead to enamel lesions, caries and inflammation of the gums.

Several studies investigated and confirmed the caries-preventive effect of Cervitec in patients undergoing orthodontic treatment [7; 38-46].

Kronenberg O, Lussi A. (2009): Preventive effect of ozone on the development of white spot lesions during multibracket appliance therapy.

Kronenberg *et al.* analyzed the efficacy of various treatments to prevent enamel demineralization in orthodontic patients. Twenty patients with fixed orthodontic appliances and poor oral hygiene were recruited into this split mouth study. The four quadrants of each patient were either treated with ozone (which has a toxic effect on bacteria) or with a combination of Cervitec and Fluor Protector or they served as control. The Visible Plaque Index (VPI) and enamel demineralization were evaluated clinically. The average VPI of all four quadrants was 55.6%. New, clinically visible enamel demineralization was observed in only 0.7% of the areas evaluated after the treatment with Cervitec/Fluor Protector. White spot formation was significantly lower in these quadrants than in the quadrants treated with ozone (3.2%). Consequently, caries protection is higher after the treatment with Cervitec/Fluor Protector compared to ozone or no treatment at all [40].

Kneist S, Zingler S, Lux C. (2008): Therapiebegleitende Massnahmen zur Kontrolle des Karies- und Demineralisationsrisikos bei kieferorthopädischer Behandlung.

In a study involving adolescents undergoing orthodontic treatment, Kneist *et al.* showed that the levels of mutans streptococci can be clearly reduced by applying Cervitec varnish (three applications in one week) (see Figure 11). While 90% of the patients were in a high caries risk class (SM 2 and 3) at the beginning of the study, this figure decreased to 40% due to the application of Cervitec. However, the bacterial counts increased fairly quickly after application of the varnish – after only two weeks, the mutans streptococci counts indicated again a high caries risk (> 80% of the patients were classified as SM 2 or 3).

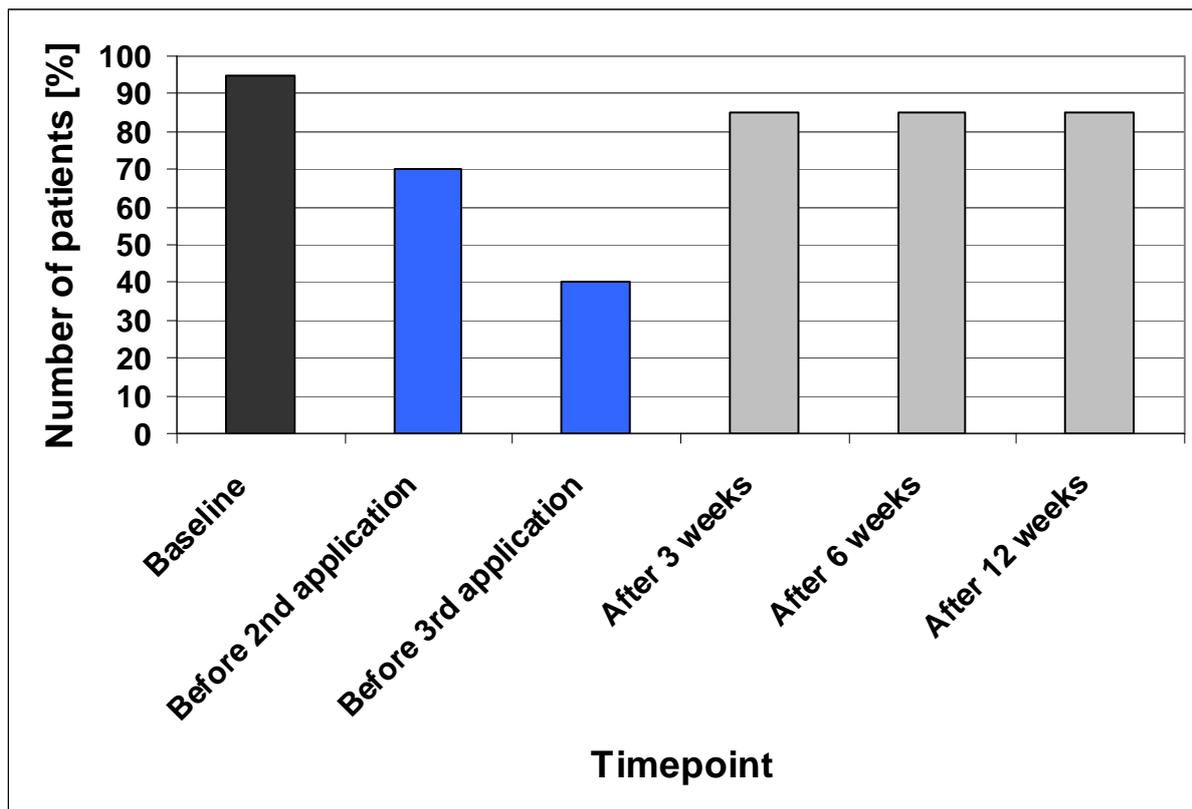


Figure 11: Number of orthodontic patients with high bacterial counts (SM counts of 2 and 3 in CRT bacteria tests) undergoing treatment with Cervitec. Young orthodontic patients wearing removable appliances were treated with Cervitec at an interval of two to three days. The bacterial count was determined using CRT bacteria tests. The number of patients with a high bacterial count (SM 2 and SM 3) clearly decreased during the period of the Cervitec treatment. After three weeks, however, extensive bacterial recolonization was observed.

Adapted from Kneist et al, 2008

The authors rated the properties of Cervitec particularly high because it does not cause discoloration. Neither in adolescents with removable appliances nor in adolescents with fixed devices was a change in the tooth shade observed after the application of Cervitec varnish, while the use of the CHX-containing mouth rinse Oral-B and the CHX gel Corsodyl caused severe discoloration (see Figure 12) [39].

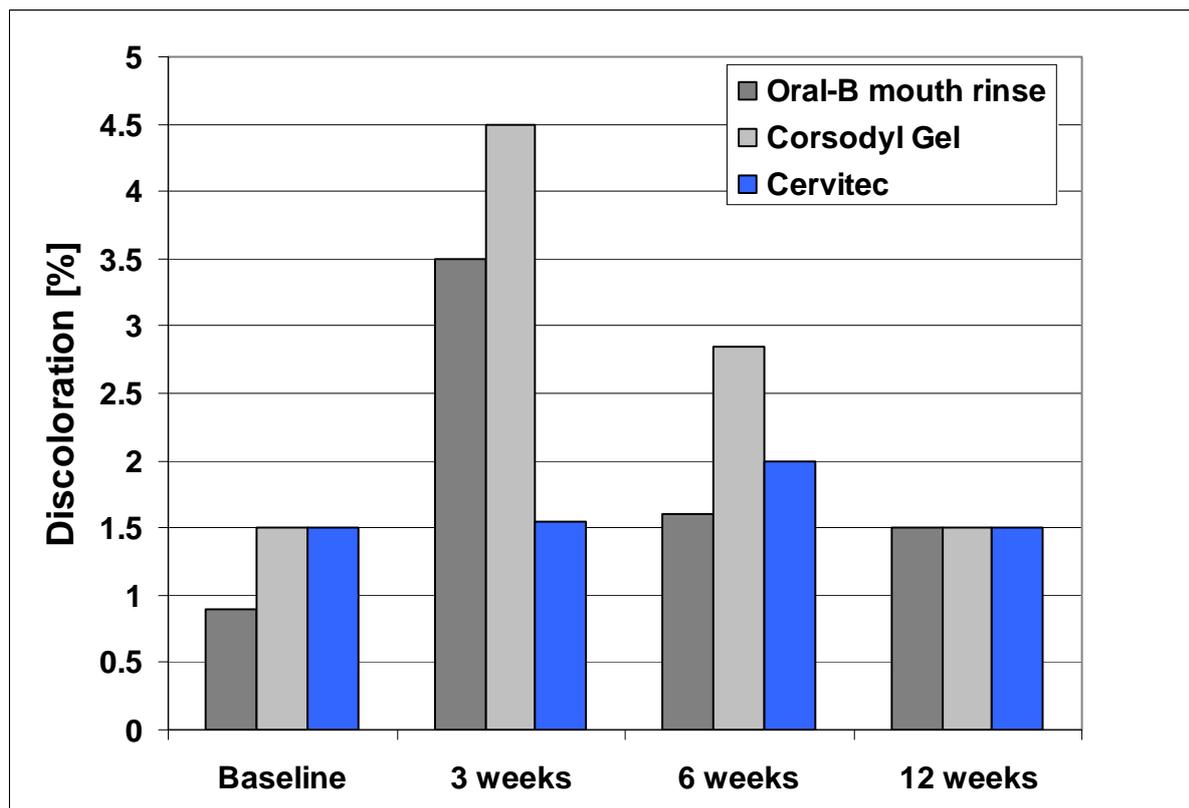


Figure 12: Discoloration after the use of CHX-containing products. Young orthodontic patients with fixed appliances used different CHX-containing products (Oral B mouth rinse: three weeks, two times a day for one minute, 49 patients; Corsodyl gel: three weeks, two times a day for five minutes, 37 patients; Cervitec: three days, 30 patients). During the observation period of twelve weeks, the discoloration of teeth was evaluated. The CHX mouth rinse and gel lead to severe staining after three weeks, while Cervitec varnish did not cause a change in the tooth shade.

Adapted from Kneist et al, 2008

Derks A, Frencken J, Bronkhorst E, Kuijpers-Jagtman AM, Katsaros C (2008): Effect of chlorhexidine varnish application on mutans streptococci counts in orthodontic patients.

In this study, 80 adolescents wearing fixed orthodontic appliances were divided into four groups and treated with different CHX regimens: application of a 40-% CHX varnish (EC40, Biodent) at intervals of either one month, two months or three months or application of Cervitec (1% CHX, 1% thymol) at two-month intervals. The caries risk was assessed on the basis of the mutans streptococci count in the plaque. For this purpose, the bacteria contained in the plaque samples were grown on a selective agar medium, which only allowed the growth of mutans streptococci. A follow-up examination of 60 patients revealed that the mutans streptococci counts were lower in the cases treated with the 40-% varnish compared to Cervitec. However, a difference in the efficacy of the two varnishes was no longer detectable after two months [47].

Øgaard B, Larsson E, Henriksson T, Birkhed D, Bishara S (2001): Effects of combined application of antimicrobial and fluoride varnishes in orthodontic patients.

Two hundred and twenty adolescents were treated either with Cervitec and Fluor Protector or only with Fluor Protector every twelve weeks for the duration of wearing fixed orthodontic appliances (72 weeks). Another 100 adolescents who did not receive any varnish treatment served as a control group. Cervitec was shown to significantly reduce the MS count in plaque in the first 48 weeks and at the time of debonding. The combination of a fluoride and a chlorhexidine varnish tended to be more effective at preventing the development of new

primary caries lesions in the upper incisors than the treatment with a fluoride varnish alone [43].

M. Madléna, S. Marton, G. Nagy (2000): Effect of chlorhexidine varnish on bacterial levels in plaque and saliva during orthodontic treatment.

Madléna *et al.* examined the effect of Cervitec on the bacterial composition in the plaque of orthodontic patients in a split mouth study. Twenty-four patients aged between 14 and 18 were treated with Cervitec or a placebo varnish after the brackets had been placed. The application was repeated every three months. The bacterial counts were evaluated in the saliva and plaque at baseline and after one, three, six, nine and twelve months using Dentocult. After the application of Cervitec, the number of plaque samples with low mutans streptococci counts significantly increased compared with those treated with a placebo varnish (see Figure 13). Moreover, the number of new carious lesions found after debonding the brackets was significantly higher in the placebo group than in the Cervitec group [7].

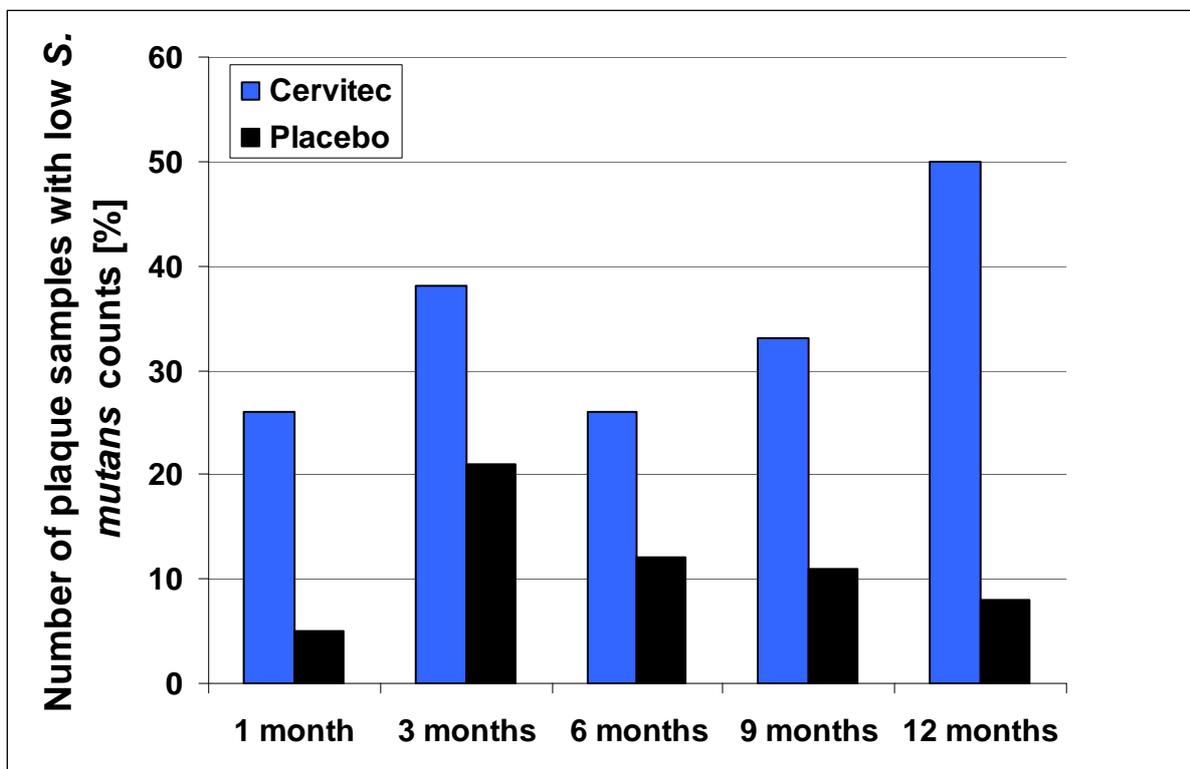


Figure 13: Reduction of mutans streptococci in plaque. Young orthodontic patients with fixed appliances were treated with Cervitec or a placebo. The level of mutans streptococci in the plaque was evaluated using Dentocult. Cervitec resulted in a clear increase in the number of plaque samples with low MS counts, while the placebo only marginally affected the bacterial composition of the plaque.

Adapted from Madléna et al, 2000

Eronat C, Alpöz AR (1997): Effect of Cervitec varnish on the salivary Streptococcus mutans levels in the patients with fixed orthodontic applications.

A single application of Cervitec significantly reduced the mutans streptococci count in the saliva of patients with fixed orthodontic appliances. In order to obtain the best possible antibacterial effect, the varnish should be applied at three-month intervals. This information was obtained in a study involving 80 participants. No reduction was noted when a placebo varnish was applied [38].

Øgaard B, Larsson E, Glans R, Henriksson T, Birkhed D (1997): Antimicrobial effect of a chlorhexidine-thymol varnish (Cervitec) in orthodontic patients.

When Cervitec is applied before the brackets are bonded, the number of mutans streptococci in plaque is significantly reduced. In this six-month study involving 198 adolescents, the increase in bacteria was significantly lower in the test group five months after the brackets were bonded than in the members of the control group, who were only treated with the fluoride varnish Fluor Protector every twelve weeks [41].

Sköld K, Twetman S, Hallgren A, Yucel-Lindberg T, Modeer T (1998): Effect of a chlorhexidine/thymol-containing varnish on prostaglandine E2 levels in gingival cervical fluid.

In this study of patients with fixed orthodontic appliances and gingivitis, the results 30 days after the application of Cervitec showed a general decrease in gingival bleeding and inflammation. The amount of gingival cervical fluid significantly decreased and the concentration of the inflammatory mediator PGE2 was also reduced [44].

4.2.8 Exposed root surfaces and gerodontics

Root caries may occur in teeth with a lengthened clinical crown, i.e. when there has been recession of the gingival tissue leading to exposure of the root surface, which is then colonized by microorganisms. The occurrence of root caries increases with age. The prevalence of root caries in the remaining dentition of patients over 60 years of age and residents of homes for the elderly ranges between 60 and 90% [19]. Moreover, these patients often take medication that reduces salivary flow (tranquilizers, antihypertensive and antihistamine drugs), which increase the caries risk.

The antimicrobial and caries-inhibiting effect of Cervitec on exposed root surfaces has been investigated in various clinical trials. It was found that the application of Cervitec leads to a reduction in mutans streptococci numbers [48-56]. While the study of Baca *et al.* [57] and of Brailsford *et al.* [51] revealed that Cervitec represented a genuine benefit to the elderly patients with root caries, the study conducted by Johnson and Almqvist did not produce a conclusive result [50].

Baca P, Clavero J, Baca AP, Gonzalez-Rodriguez MP, Bravo M, Valderrama MJ (2009): Effect of chlorhexidine-thymol varnish on root caries in a geriatric population: A randomized double-blind clinical trial.

This double blind, randomized study included 68 people, who were living in homes for the elderly in Almeria (Spain). The patients were split into two groups of 34 volunteers each. Cervitec or a placebo varnish was applied in each volunteer twice during the first week of the study and then after one, three, six, nine and twelve months. At the end of the study (after twelve months), it was possible to re-examine 21 patients with totally 60 root caries lesions from the Cervitec group and 25 patients with totally 65 lesions from the placebo group. In the Cervitec group, the increase in height and width of the caries lesions was statistically significantly lower after six and twelve months compared to the placebo group (see Figure 14). On average, 0.67 new lesions were found in the Cervitec group after twelve months and 1.32 in the placebo group. Also, changes in the shade and texture of the lesions were more beneficial in the Cervitec group than in the control group; in some cases they even changed for the better [57].

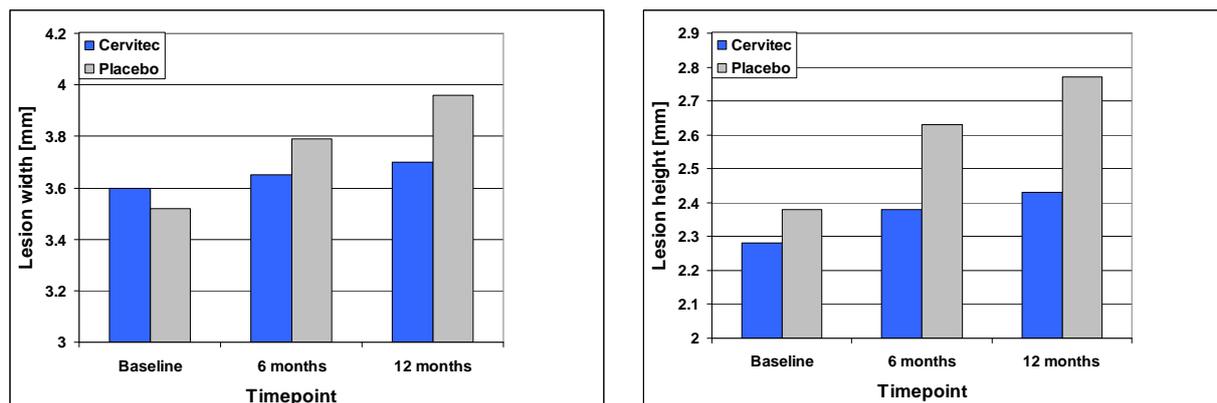


Figure 14: Progression of the clinical parameters of root caries after the application of Cervitec and a placebo gel. Elderly patients with root caries were treated with Cervitec or a placebo varnish several times. The width (chart on the left) and height (chart on the right) of the lesions were evaluated at baseline and after six and twelve months. At baseline, no statistically significant differences between the groups were observed. In the course of the study, both parameters deteriorated in the placebo group, while the treatment with Cervitec lead to a statistically significant reduction in the increase in the width and height of the lesions.

Adapted from Baca et al, 2009

Clavero J, Baca P, Gonzalez MP, Valderrama MJ (2006). Efficacy of chlorhexidine-thymol varnish (Cervitec®) against plaque accumulation and gingival inflammation in a geriatric population.

A similar study, previously conducted by the same authors, examined the effect of Cervitec on the accumulation of plaque and inflammation of the gums in elderly people living in residential care homes. The study was carried out over a period of six months; Cervitec or a placebo varnish was applied every three months. At the end of the study, the oral health of 56 patients could be evaluated. Over the period of the study, the treatment with Cervitec resulted in a statistically significant reduction in the gingiva index; however the plaque index remained unchanged [58].

Brailsford SR, Fiske J, Gilbert S, Clark D, Beighton D (2002): The effects of the combination of chlorhexidine/thymol- and fluoride-containing varnishes on the severity of root caries lesions in frail institutionalised elderly people.

In this study, which involved 102 patients between the ages of 78 and 87, the clinical effect of the application of Cervitec in combination with Fluor Protector (group B) on the progression of root caries lesions was investigated and compared to a control group (group A, Fluor Protector only). The study showed that this combination improves the clinical status of active root caries lesions. The increase in the lesion depth is significantly higher if Fluor Protector is applied alone than if it is applied in combination with Cervitec. The same applies to the lesion width (see Figure 15) [51].

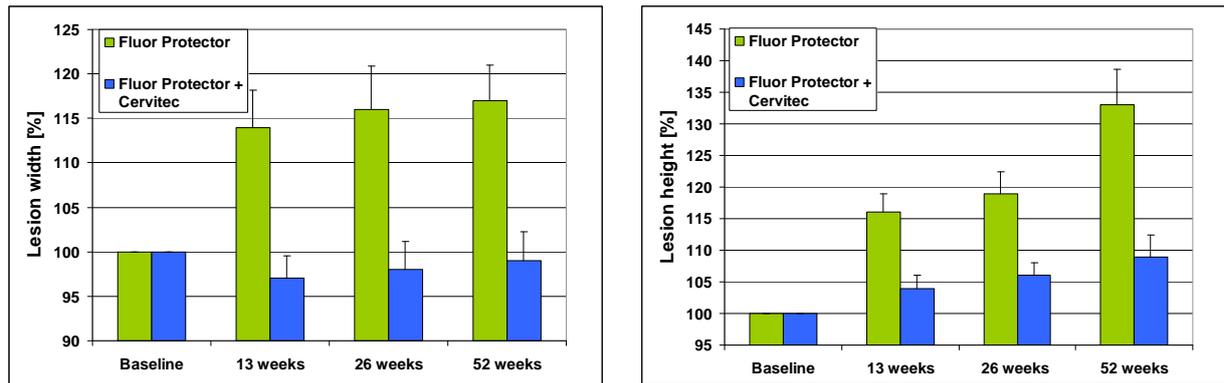


Figure 15: Progression of the clinical parameters of root caries after application of Fluor Protector or Fluor Protector and Cervitec. Elderly patients with root caries were repeatedly treated with Fluor Protector or a combination of Fluor Protector and Cervitec. The width (chart on the left) and height (chart on the right) of the lesions were evaluated at baseline and after 13, 26 and 52 weeks. Over the course of the study, both parameters deteriorated in the group that received Fluor Protector only, whereas the combined treatment with Fluor Protector and Cervitec resulted in a statistically significant reduction in the increase of the lesion width and height.

Adapted from Brailsford et al, 2002

Ekenbäck BS, Linder LE, Lönnies H (2000): Effect of four dental varnishes on the colonization of cariogenic bacteria on exposed sound root surfaces.

In this six-month clinical study, Cervitec was shown to significantly reduce the number of mutans streptococci in the plaque of healthy tooth necks. However, it did not change the composition of plaque. The lactobacilli and overall streptococci counts remained unchanged. Thymol alone or a variety of fluoride preparations did not influence the mutans streptococci, lactobacilli or the entire streptococci count [52].

Schmeiser R, Schiffner U, Gülzow HJ (1994): Auswirkungen eines chlorhexidinhaltigen Lackes auf die Dentindemineralisation unter experimenteller Plaque.

Dentin samples from the root area were exposed to mutans streptococci and demineralizing and remineralizing conditions in an artificial oral cavity for six weeks on a daily basis. While untreated controls showed demineralized areas of 13 µm in depth, samples treated with Cervitec did not demonstrate any lesions or considerably shallower ones [53].

4.2.9 Protection of restorations and implants

4.2.9.1 Restoration margins

Secondary caries may lead to the loss of restorations. Restoration margins, in particular crown and bridge margins, represent potential plaque retentive areas. Selective application of antimicrobial preparations such as Cervitec can be an invaluable preventive measure, contributing to the long-term success of the restoration.

Wallman C, Birkhed D (2002): Effect of chlorhexidine varnish and gel on mutans streptococci in margins of restorations in adults.

In this study, 18 patients with extensive reconstructions and increased bacterial burden (>250,000 cfu/ml of saliva) were either treated with Cervitec, a placebo or chlorhexidine gel. The plaque samples taken from the restoration margins were examined for their contents of mutans streptococci. It was found that in contrast to the placebo varnish, the application of Cervitec significantly reduced the colonization of the margins by mutans streptococci (see Figure 16) [59].

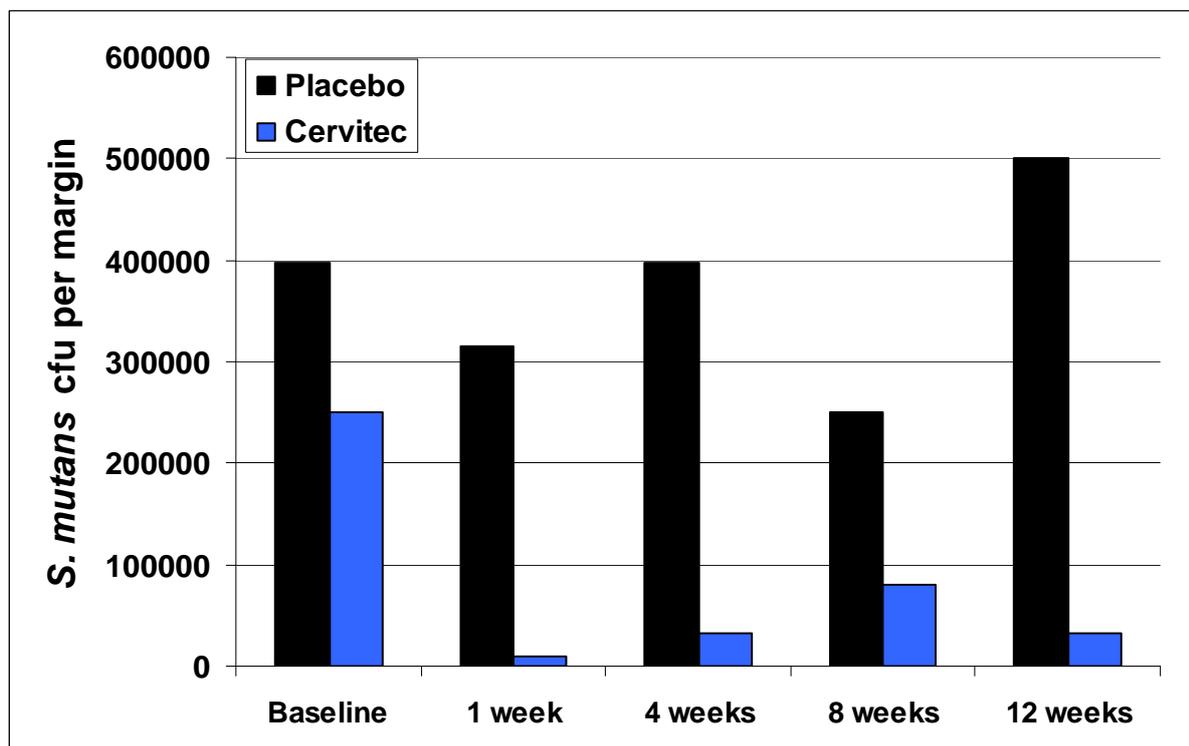


Figure 16: Reduction of mutans streptococci in the margins of restorations after application of Cervitec. Cervitec or a placebo were applied each to six patients, who had numerous restorations. The products were applied twice at an interval of three to four days. Plaque samples were collected from eight to nine restoration margins of each volunteer and examined for their contents of mutans streptococci. In contrast to the placebo varnish, Cervitec resulted in a clear reduction in mutans streptococci numbers.

Adapted from Wallman et al, 2002

4.2.9.2 Interaction with dental adhesives

Several studies have investigated the effect of Cervitec on the bond strength of adhesives on enamel [60; 61]. As expected, it was found that placing Cervitec on acid-etched enamel prior to the application of adhesive, or mixing Cervitec with the adhesive resulted in significantly lower bond strength values.

Ivoclar Vivadent strictly recommends users to avoid mixing Cervitec or Cervitec Plus with adhesives or other luting materials, or applying them to acid-etched enamel surfaces during adhesive cementation procedures.

4.2.9.3 Implants

Johansson LA, Ekfeldt E, Petersson LG, Edwardsson S (1994): Antimicrobial effect of a chlorhexidine varnish, Cervitec in healing caps in osseointegrated prosthetic treatment [62]

Cervitec was placed in healing caps for implants. Patients received caps with Cervitec as well as non-prepared placebo caps. The study found that all the placebo caps were substantially colonized with various types of bacteria. Cervitec caps demonstrated very little colonization. In two cases, lactobacilli were isolated. Patients verified this finding with olfactory proof - the caps treated with Cervitec had no disagreeable smell.

Besimo CE, Guindy JS, Lewetag D, Meyer J (1999): Prevention of bacterial leakage into and from prefabricated screw-retained crowns on implants *in vitro*.

Besimo CHE, Guindy JS, Lewetag D, Besimo RH, Meyer J (2000): Marginale Passgenauigkeit und Bakteriendichtigkeit von verschraubten implantatgetragenen Suprastrukturen.

Many microorganisms, e.g. *S. aureus*, are capable of overcoming the gap between the crown and implant and to grow in that area. The colonization of an implant with *S. aureus* may result in peri-implantitis, which may jeopardize the survival of the implant. The authors of the above studies examined thirty Ha-Ti implant-crown-reconstructions for ingress of bacteria into the inside of the implant after they had been sealed with Cervitec. At each stage of the study, five test specimens were collected and examined for infiltration with *S. aureus*. In control test specimens, which had not been sealed with Cervitec, *S. aureus* was detected on the insides of all test samples after both complete immersion (marginal gap and screw hole in liquid) and partial immersion (without screw hole) after 48 hours at the latest (complete immersion) and 120 hours (partial immersion). By contrast, *S. aureus* was observed in only one of the five test specimens that had been sealed with Cervitec and completely immersed in liquid for four weeks, whereas *S. aureus* was not found in any of the other Cervitec samples, which were incubated for three, five, six, seven and eight weeks. None of the 30 Cervitec test samples which had only been immersed up to below the screw hole and incubated for three to eleven weeks were contaminated with *S.aureus* on the inside surfaces (see Figure 17). Cervitec is thus capable of protecting implants from bacterial colonization and reducing the risk of peri-implantitis [63; 64].

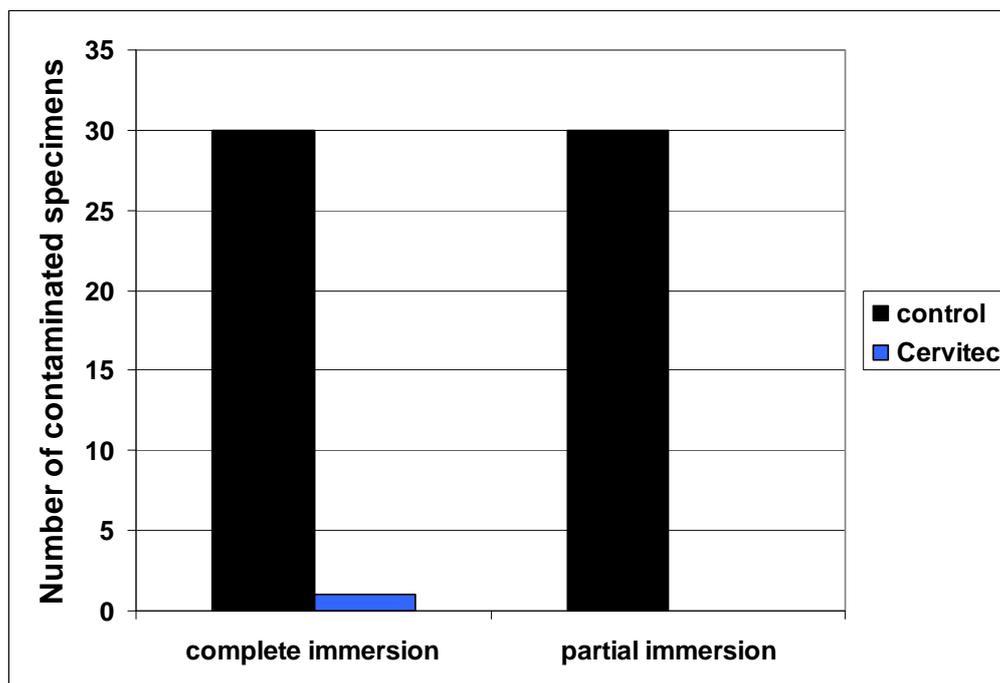


Figure 17: Reduction in bacterial infiltration in implant components after the application of Cervitec. Thirty implant test specimens were sealed with Cervitec and another 30 were left untreated. Then, the test specimens were incubated in a bacterial solution for up to eleven weeks. The test specimens were either completely ("marginal gap and screw hole") or partially (up to the marginal gap) immersed in the solution. All unsealed implant test specimens were colonized by bacteria, whereas the sealing prevented the ingress of bacteria in (almost) all implants.

Adapted from Besimo et al, 1999 & 2000

5. Biocompatibility

5.1 Toxicological data

5.1.1 Acute oral toxicity

The acute oral toxicity of the ingredients of Cervitec Plus is shown in the table below:

Component	LD50 ORL-RAT	Ref
Acrylate co-polymer	>10000 mg/kg	(1)
Vinyl acetate co-polymer	>10000 mg/kg	(2)
Thymol	980 mg/kg	(3)
Chlorhexidine diacetate	2000 mg/kg	(4)

The toxicity of the main quantitative ingredients (acrylate co-polymer, vinyl acetate co-polymer) is limited. Given the moderate toxicity and low contents of thymol and chlorhexidine diacetate in Cervitec, a toxicological risk through oral absorption is not present.

5.1.2 Acute local toxicity (tissue compatibility and irritation)

The irritation potential of the acrylate co-polymer and the vinyl acetate co-polymer have been evaluated by the Cosmetic Ingredient Review Expert Panel. No irritation potential was identified for either of the products (1, 2).

Chlorhexidine has been classified as non-irritant. Thymol has been classified as etching (5). Skin irritation tests in the rabbit were conducted with the original Cervitec formula, which contains the same concentrations of chlorhexidine diacetate and thymol. No irritation potential was detected (6). These findings are also supported by long-term clinical experiences.

5.1.3 Cytotoxicity

Compared to Cervitec, only the varnish base has been changed in Cervitec Plus, whereas the concentrations of chlorhexidine and thymol have remained unchanged. Therefore, only the cytotoxicity of the varnish component was investigated. For this purpose, the dried varnish was examined for cytotoxicity. The dried varnish was tested in a XXT assay according to ISO 10993-5. No cytotoxicity was observed (7).

5.1.4 Genotoxicity

Acrylate co-polymer and vinyl acetate co-polymer are frequently employed in the cosmetic and pharmaceutical industry. The genotoxicity of these two co-polymers was analyzed (1, 2). None of the two polymers showed genotoxic effects in the AMES test or in eukaryotic assays.

To test the genotoxicity of the varnish base, the varnish component (consisting of ethanol, water and both co-polymers) was dried and examined in the AMES test. No genotoxic potential was observed in this testing system (8).

Thymol is negative in the AMES test and negative in the *in vivo* micro-nucleus test in mice (9).

The mutagenicity of chlorhexidine diacetate has been evaluated by the US Environmental Protection Agency (EPA) (10). In a series of eukaryotic mutagenicity tests, no evidence could be found to suggest a mutagenic effect. According to the summary report of the European

Medicines Agency (EMA), cancerogenicity studies conducted with mice and rats did not provide evidence to suggest a cancerogenic effect of chlorhexidine (4).

Based on the data available, it can be assumed that Cervitec Plus does not pose an increased risk of DNA damage.

5.1.5 Sensitization

Contact hypersensitivity tests (maximization tests) were conducted with the original Cervitec formula in rabbits. They did not reveal a sensitizing effect under the test conditions (11).

The newly employed substances, acrylate co-polymer and vinyl acetate co-polymer, have been evaluated with regard to their sensitizing potential. Both materials have not shown a sensitization potential (1, 2).

5.2 Summary and conclusions

No toxic, mutagenic, sensitizing or irritant effect has been observed with Cervitec Plus.

According to the current state of knowledge, it can be concluded that Cervitec Plus is biocompatible and toxicologically harmless when used correctly.

5.3 Literature on biocompatibility

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