

ViziLite® Plus

DEVICE DESCRIPTION:

ViziLite Plus consists of the ViziLite, used as an adjunct to visual examination of the oral mucosa with incandescent light for identification of oral mucosal abnormalities, and the TBlue^{630™} (Zila Tolonium Chloride (ZTC™)) Oral Lesion Marking System, to further assist with the evaluation and monitoring of ViziLite-identified white oral mucosal abnormalities in patients at increased risk for oral cancer.

ViziLite Plus is a visualization system that is intended as an adjunct to conventional visual examination with incandescent light of oral mucosa and employs the same components and mechanism of action as the previously cleared ViziLite Test Kit (a.k.a. ViziLite Comprehensive Exam Tray and the OralLite Test Kit and Acetic Acid Rinse) and is indicated for the same patient population and intended use. Neither the ViziLite examination light source, nor the 1% Acetic Acid Rinse, have been changed or significantly modified for production of ViziLite Plus.

The TBlue⁶³⁰ Oral Lesion Marking System consists of three swab components: two swabs of Acetic Acid solution, and one swab with TBlue⁶³⁰ (ZTC) solution, which is similar to the metachromatic vital dye known as toluidine blue. The application of the dye to ViziLite-identified white oral mucosal lesions during clinical trials was able to assist with evaluation, monitoring, and tissue sampling, physically marking 51% of the ViziLite-identified white lesions and allowing the health care provider to better visualize those lesions without the use of chemiluminescent light (ViziLite).

The TBlue⁶³⁰ Oral Lesion Marking System contains 1% Acetic Acid Rinse (with the inactive ingredients: Purified Water, USP; Sodium Benzoate, NF; and Raspberry Flavor) and the 0.5% Zila Tolonium Chloride solution (with the inactive ingredients Purified Water, USP; Acetic Acid, USP; Sodium Acetate, NF; Hydrogen Peroxide, 30%, USP; SD 18 Ethyl Alcohol; and Raspberry Flavor).

PRINCIPLE OF ACTION:

ViziLite:

Following the application of a cytoplasmic dehydration agent such as an acetic acid solution, leukoplakic lesions are better visualized due to changes in their refractile properties. This occurs in atypical non-keratinized squamous epithelium due to an increase in the nuclear: cytoplasmic ratio of the cells.

Adding diffuse chemiluminescent light (Speculite) to a conventional projected incandescent light examination of the cervical squamous epithelium has been clinically shown to increase the detection of biopsy proven squamous cell dysplasia and malignancy when compared with detection by the unaided eye and detection with magnified visualization with incandescent light.

CLINICAL STUDIES:

A clinical study was conducted with patients presenting with known oral leukoplakia or erythroleukoplakia as well as patients who previously had oral cancer and were at risk for recurrence. ViziLite identified 102 lesions. Ninety two of the 102 lesions found in 85 patients were biopsied, sent for pathology diagnosis and the results are listed in Table 1. Ten lesions were not biopsied because they had been biopsied within a one-year period of the time of the current study examination, and because there had been no change in the appearance of these lesions.

Table 1. Biopsy Diagnoses of ViziLite Identified Lesions

Pathology Diagnosis	Number
Normal tissue	2
Benign Leukoplakia	1
Inflammatory Abnormality	17
Hyperkeratosis/atypia	21
Lichen Planus	6
Mild dysplasia	14
Moderate Dysplasia	13
Severe Dysplasia (carcinoma-in-situ)	10
Squamous cell cancer	8

Forty-five of the 92 lesions (49%) were determined to be atypical, i.e. mild dysplasia, moderate dysplasia, severe dysplasia (carcinoma-in-situ) or squamous cell carcinoma. The remaining 47 biopsies were considered not to have pathology. The correlations between the TBlue⁶³⁰ exam results and the biopsy results of the 92 lesions identified by ViziLite are presented in Table 2.

In Table 2, it can be seen that 47 lesions met the criteria for being considered positive for TBlue⁶³⁰ staining (TBlue⁶³⁰ exam positive), with 32 of these lesions expressing some dysplasia (68.1% PPV). Of the 45 lesions shown dysplastic on biopsy (exam positive or negative), the TBlue⁶³⁰ Oral Lesion Marking System identified 32 of them (71% PPV).

The 13 ViziLite positive cases that were missed (TBlue⁶³⁰ negative, but biopsy positive) consisted of 8 mildly dysplastic and 5 moderately dysplastic lesions.

Table 2. Correlation of Biopsy Results with the TBlue⁶³⁰. Examination Results

	Mucosal Biopsy Results (for Any Dysplasia) of ViziLite Positive Lesions	
TBlue⁶³⁰ Exam Result	Biopsy positive	Biopsy negative
TBlue⁶³⁰ exam positive	32	15
TBlue⁶³⁰ exam negative	13	32

All 10 cases of severe dysplasia (carcinoma-in-situ) and all 8 cases of squamous cell cancer were identified with the addition of the TBlue⁶³⁰ Oral Lesion Marking System adjunct to the ViziLite.

INTENDED USE:

The ViziLite Plus with ViziLite and the TBlue⁶³⁰ Oral Lesion Marking System are intended for use only as adjuncts to the conventional oral mucosal examination with incandescent light.

The ViziLite examination, using chemiluminescent light, is intended only as an adjunct to traditional oral examination by incandescent light to improve identification, evaluation and monitoring of white oral mucosal abnormalities in populations at increased risk for oral cancer.

The TBlue⁶³⁰ Oral Lesion Marking System, as supported by clinical trials, is provided to health care professionals as an adjunct to the ViziLite examination and assists in the further evaluation of ViziLite-identified white oral mucosal lesions for patients at an increased risk for oral cancer.

The TBlue⁶³⁰ Oral Lesion Marking System is *not* intended to be used as an initial screening examination for identification and evaluation of oral mucosal abnormalities, nor is it intended to replace initial conventional screening under incandescent light, ViziLite examination, or biopsy. The marking system is not intended to be used as an indicator of lesions warranting further study, including biopsy. Whether a lesion is marked with the dye or not should not alter the clinician’s clinical behavior as dictated by the results of the ViziLite examination. The marking dye, when positive, acts as a lesion marker that allows for the removal of the ViziLite device while preserving the anatomic character of the lesion.

INDICATIONS FOR ViziLite PLUS:

ViziLite Plus consists of the ViziLite and the TBlue⁶³⁰ Oral Lesion Marking System.

ViziLite is a chemiluminescent light source system indicated for use as an adjunct to conventional oral mucosal screening by trained health care providers for the identification, evaluation, and monitoring of oral mucosal abnormalities in a population at increased risk for oral cancer.

The TBlue⁶³⁰ Oral Lesion Marking System, is a three-component swab system which is indicated as an adjunct to the ViziLite Test for oral mucosa lesions, for further evaluation and monitoring of ViziLite-identified white lesions in a population at increased risk for oral cancer.

The TBlue⁶³⁰ Oral Lesion Marking System is not being proposed for use in the initial oral mucosal examination without initial lesion identification with ViziLite. Furthermore, the TBlue⁶³⁰ Oral Lesion Marking System is not intended to be used as an indicator of lesions warranting further study, including biopsy. Whether a lesion is marked with the dye or not should not alter the clinician’s clinical behavior as dictated by the results of the ViziLite examination. The marking dye, when positive, acts as a lesion marker that allows for the removal of the ViziLite device while preserving the anatomic character of the lesion.

CONTRAINDICATIONS:

The ViziLite examination is an adjunct to conventional oral examination with incandescent light and should not be used without first performing a conventional examination.

The TBlue⁶³⁰ Oral Lesion Marking System is not intended to be used without prior traditional oral visual examination using ambient projected light followed by a ViziLite examination.

The TBlue⁶³⁰ Oral Lesion Marking System is not intended for “initial identification” of abnormalities of the oral mucosa, but is provided to the health care professional as an adjunct to the already cleared ViziLite for the evaluation, monitoring, and sampling of “ViziLite-identified lesions” in patients identified as increased risk for oral cancer.

The TBlue⁶³⁰ Oral Lesion Marking System is contraindicated in patients with a known history of hypersensitivity to any of the ingredients or their analogs.

The TBlue⁶³⁰ Oral Lesion Marking System is contraindicated in patients who are pregnant or lactating.

Due to the lack of safety data, the TBlue⁶³⁰ Oral Lesion Marking System should not be used in children, patients with liver or renal insufficiency, or patients with difficulty swallowing.

The TBlue⁶³⁰ Oral Lesion Marking System should be used with caution in patients who may have difficulty following directions during the lesion staining procedure (e.g. patients with severe physical or mental disabilities).

WARNING/PRECAUTIONS- ViziLite:

To prevent swallowing or choking:

The health care provider should ensure that the activated ViziLite is firmly inserted into the provided ViziLite retractor before placing it into the patient's mouth.

The health care provider should hold the ViziLite retractor firmly while it is placed inside the patient's mouth.

To prevent potential leakage of ViziLite chemicals into the mouth:

Inspect the ViziLite for any evidence of chemical leakage prior to capsule activation. Discard any capsule that does not appear to be intact.

Inspect the activated ViziLite for potential leakage before placing it in to the patient's mouth for ViziLite.

Do not use a capsule for ViziLite if the capsule does not appear to be intact or functioning properly.

[Note: The chemiluminescent chemicals and the materials used in the manufacturer of the ViziLite have been shown to be non-toxic in animal studies should they be either swallowed or applied to the epithelial surface. Therefore, ViziLite should not present a significant risk to humans when used as a light source for oral examination under usual conditions. However, oral exposure to the contents of the ViziLite may cause transient irritation to the mouth, throat and gastrointestinal tract.]

[Remedy for accidental exposure to chemicals: Rinse mouth immediately and dilute with 4 to 5 ounces of milk or water. Decontamination with syrup of ipecac, activated charcoal or gastric lavage is not indicated.]

After 10 minutes, the chemiluminescent light begins to fade and the ability to visualize white lesions will also decrease. Therefore, perform the examination of oral tissues within 10 minutes of the ViziLite activation.

ViziLite is to be used as an adjunct to conventional oral examination.

ViziLite is not intended to be used for grading acetowhite lesions.

All activated and/or used ViziLite units must be discarded in a proper receptacle per the procedures of the facility.

ViziLite is intended as a disposable, single use patient device.

ViziLite is not reusable.

WARNING PRECAUTIONS- ViziLite Rinse:

ViziLite is intended as a disposable, single use patient device.

ViziLite is not reusable.

ViziLite Rinse is not intended to be swallowed.

ViziLite Rinse is intended for oral use only. Keep out of reach of children.

Do not refrigerate ViziLite Rinse.

WARNINGS/PRECAUTIONS- TBlue⁶³⁰ Oral Lesion Marking System:

No severe adverse reactions are expected when the TBlue⁶³⁰ Oral Lesion Marking System is used according to package instructions. Some patients may find the taste of the product unappealing and may gag. Patients may also experience a slight burning sensation of the oral mucosa due to the acetic acid.

Removable oral prostheses should be removed and any associated trauma or inflammation given time to heal prior to use of the product.

Patients should be informed prior to the TBlue⁶³⁰ procedure that there may be a residual bluish discoloration on the vermillion border, dorsum of the tongue, and dental plaque, which usually wears off in 2-6 hours. Staining in these areas with the Zila Tolonium Chloride is normal and should not be considered a positive result in the absence of clinical suspicion.

Care should be taken to protect clothing, as well as equipment and environmental surfaces from being stained. The patient should be advised of the possibility of this effect, and assured that the color change is temporary.

Should any of the material be accidentally swallowed, the urine and and/or stools may be colored temporarily blue-green or blue, respectively. The patient should be

advised of the possibility of this effect, and assured that the color change is temporary. The patient may also be instructed to contact his/her examining physician/dentist if this occurs.

Common restorative materials including porcelain, composites, and acrylics are not known to stain permanently.

INTERACTIONS:

Interactions of the TBlue⁶³⁰ Oral Lesion Marking System components with other medications have not been studied, but are unlikely.

PREGNANCY AND LACTATION:

The TBlue⁶³⁰ Oral Lesion Marking System is contraindicated for use in pregnant women. There have been no well controlled studies in pregnant women to know the safety of use in this population.

The TBlue⁶³⁰ Oral Lesion Marking System is contraindicated for lactating women. It is not known whether Zila Tolonium Chloride is excreted in human breast milk.

ADVERSE EVENTS:

None Known.

OVERDOSAGE:

No adverse events have been reported in the published literature concerning the use of Tolonium Chloride in the mouth for staining oral lesions. The TBlue⁶³⁰ Oral Lesion Marking System contains a Zila Tolonium Chloride dye swab with 7mg of Zila Tolonium Chloride, which conservatively yields an exposure of approximately 0.1mg/kg (based on a 60kg person). Reports from published studies indicate physiological alterations are not observed at dose levels below 5 mg/kg administered intravenously. Some patients, receiving 100 mg commercially available toluidine blue orally in capsule form three times daily, reported nausea. The NOAEL (No-Observable-Adverse-Effect Level) determined in toxicology studies on orally administered toluidine chloride was 20mg/kg in rats and was 15 mg/kg in rabbits. Data regarding Zila Tolonium Chloride and toluidine blue toxicity are available upon request.

GENERAL PROCEDURE for ViziLite Plus:

The ViziLite examination consists of visualization of leukoplakic areas using a diffuse chemiluminescent light source. Following conventional oral examination

with incandescent light, there is a pre-exam rinse with the ViziLite rinse, activation of the ViziLite with placement in the ViziLite retractor, dimming of the ambient light and re-examination with ViziLite. Under ViziLite, atypical or dysplastic mucosal abnormalities will appear as bright white, distinctly demarcated, and sharply marginated areas that contrast with the surrounding non-involved epithelium. Any lesion identified with ViziLite is further evaluated using the adjunctive TBlue⁶³⁰ Oral Lesion Marking System (pre- and post-acetic acid swabs and Zila Tolonium Chloride stain swab).

The TBlue⁶³⁰ Oral Lesion Marking System should only be used in conjunction with a complete oral screening exam using the ViziLite, this includes:

- 1) Conventional oral examination with overhead exam light
- 2) A 30-60 second oral rinse with ViziLite pre-rinse solution (1% acetic acid)
- 3) Examination with the ViziLite in a dim exam room
- 4) Application of the pre-dye 1% Acetic Acid solution swab
- 5) Application of the TBlue⁶³⁰ (ZTC) to any mucosal abnormalities observed.
- 6) Application of the post-dye 1% Acetic Acid solution swab

All lesions seen using ViziLite illumination are potentially important. The absence of marking by the TBlue⁶³⁰ Oral Lesion Marking System of a lesion seen with ViziLite should not preclude further analysis of the lesion, including biopsy. Any lesion seen with ViziLite may harbor pathology, and clinical judgment should always prevail when deciding the further analysis and management of these lesions

The ViziLite oral screening exam and, if indicated, application of the TBlue⁶³⁰ Oral Lesion Marking System to any mucosal abnormalities should be done before the application of any instrumentation to soft tissues. The observation, measurement and documentation of the pre-staining appearance of the oral soft tissue lesions must be completed BEFORE any observed lesions are stained with the TBlue⁶³⁰ Oral Lesion Marking System.

Instruments used in the mouth can cause minor abrasions that can retain the dye solution. In addition, areas of oral trauma (e.g. cheek bites) may show up as white lesions on the ViziLite exam and may retain the dye solution.

Before using the TBlue⁶³⁰ Oral Lesion Marking System, the patient should be draped with a bib to protect clothing. As expectoration is required, the patient should be positioned near a sink. During administration of the staining solutions, the patient should expectorate into a large (8-10 oz) cup that can be discarded as waste.

Alternatively, the contents of the cup may be poured down the center of the drain while water is running rapidly to avoid staining the sink. If the sink or any other surface becomes discolored, the stain may be removed using a soft cloth and standard hard surface cleaner, concentrated bleach, or vinegar. Environmental surfaces or objects that cannot easily be cleaned should be removed from the area or covered.

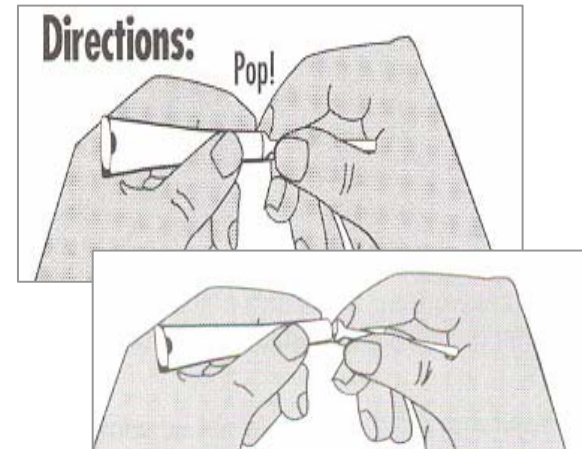
PROCEDURE for Performing the ViziLite Exam:

1. Perform a routine exam of the oral cavity - note the presence of any acetowhite lesion(s) on all oral soft tissue structures.
2. Select one (1) ViziLite acetic acid solution vial, one (1) ViziLite lightstick, and one (1) ViziLite retractor from the tray.
3. Instruct the patient to rinse their mouth with the ViziLite acetic acid solution vial (1% acetic acid solution) for up to one minute and expectorate.
4. Activate the ViziLite lightstick and assemble with the ViziLite retractor:
 - Bend the flexible lightstick, breaking brittle inner vial
 - Shake to mix the contents of the ViziLite lightstick
 - Insert the illuminated lightstick into the open piece (sheath) of the ViziLite retractor
 - Assemble the 2 pieces of the ViziLite retractor
5. Dim ambient room lights
6. Repeat the exam of the oral cavity using illumination from the ViziLite
7. Look for acetowhite lesion(s). Document the site(s) of any identified lesions on all oral soft tissue structures.
8. Remove the ViziLite device from the mouth and discard
9. Take appropriate clinical management action by either:
 - Documenting the absence of acetowhite lesion(s)
 - Documenting the presence of acetowhite lesion(s); andcontinue

with the TBlue⁶³⁰ procedure.

PROCEDURE for Staining White Oral Mucosal Lesions with the TBlue⁶³⁰ Oral Lesion Marking System:

1. After performing an examination of the oral cavity using conventional dental illumination (incandescent projected illumination), and performing the ViziLite oral exam, any mucosal abnormalities that have been identified using ViziLite can be stained with the TBlue⁶³⁰ Oral Lesion Marking System.
2. Data regarding the location, appearance, and measured size of any oral lesion(s) should be documented in the patient's medical record.
3. Only if a mucosal abnormality is identified during the ViziLite exam, can the TBlue⁶³⁰ Oral Lesion Marking System be used to demarcate the identified lesion(s) for further study or biopsy.
4. To open the swabs, pinch the tube firmly while rotating the tube until the seal is broken.
5. With the other hand, grasp applicator handle at base. Bend gently back and forth with a slight twisting motion until the entire seal is broken. Do not



excessively bend the applicator.

6. Twist gently and pull swab out slightly to be sure that the swab seal is completely broken. A small amount of solution may remain in the tube; therefore, caution is required to avoid spilling. It is recommended that the open tubes be placed upright in a small cup.

7. Dim the room lights and using the ViziLite, visualize the lesion(s). Apply swab #1, the pre-rinse acetic acid solution to the entire area of the white lesion(s). To apply, press firmly in a painting motion. Cover an area extending 2 cm in diameter around the visible lesion(s). Swab for 20 seconds. Direct the patient to expectorate the pre-rinse solution.

8. Direct the patient to rinse and gargle with water and expectorate. This step may be repeated.

9. Lightly dry the ViziLite illuminated area with a gauze sponge or a gentle stream of air, to minimize the risk of swallowing excess dye.

10. Continuing to use ViziLite illumination in a dim room, apply swab #2, the Zila Tolonium Chloride (blue dye) to the same white lesion(s) that have had the pre-dye acetic acid solution applied. Press firmly in a painting motion. Cover an area extending 2 cm in diameter around the visible lesion. Swab for 20 seconds. The dye solution should be expectorated.

11. Room lights may now be turned on, the balance of the staining/decolorization procedure and exam is to be done using conventional dental illumination.

12. Using conventional dental illumination, apply swab #3, the post-rinse swab to the stained lesion. Again, press firmly in a painting motion to apply the acetic acid solution using a reasonable mechanical effort to remove the blue stain. Completely cover the area where any blue stain appears. Swab for 20 seconds. This step may be repeated with the remaining post-dye solution (swab #3) to remove any excess dye.

13. Direct the patient to rinse and gargle with water and expectorate. This step may be repeated.

14. Using conventional dental illumination, measure the stained lesion and document the staining pattern. To evaluate a stained area during the exam, a swab saturated with either pre-rinse or post-rinse solution (1% acetic acid) may be used to attempt to remove excess dye

15. Take appropriate clinical management action by either counseling the patient that lesion(s) should be followed and schedule a future appointment; performing a biopsy of identified acetowhite lesion(s); referring the patient to an oral surgeon for further evaluation.

ViziLite	Dim or Off	Swab #1 Pre-rinse 1% acetic acid (Flavored)	swab	20 seconds
		Water	30 ml	20 seconds
ViziLite	Dim or Off	Swab #2 dye Tolonium Chloride 5 mg/ml	swab	20 seconds
Conventional Dental Illumination	On	Swab #3 Post-rinse 1% acetic acid (Flavored)	swab	20 seconds
Conventional Dental Illumination	On	Water	30 ml	20 seconds

Note: Be aware that the dye will be retained by the irregular papillar crevices on the dorsum of the tongue. Other areas that can retain the TBlue⁶³⁰ (ZTC) dye include dental plaque, gingival margins around each tooth, diffuse stain of the soft palate transferred from the retained stain on the dorsum of the tongue, and the margins of dental restorations. Acrylic restorations and appliances should be removed prior to application.

HOW SUPPLIED:

ViziLite Plus is supplied with ViziLite Test Kits and TBlue⁶³⁰ Kits Oral Lesion Marking System in a 20-pack and 40-pack configurations.

20-pack ViziLite Plus:

- 20 ViziLite acetic acid solution vials, 30 mL (1% Acetic Acid)
- 20 ViziLite lightsticks
- 20 ViziLite retractors
- 2 TBlue⁶³⁰ Oral Lesion Marking System kits, each containing:
 - 1 Acetic Acid pre-rinse solution swab, 1.3 mL (1% Acetic Acid)
 - 1 Zila Tolonium Chloride solution swab, 1.3 mL (0.5% Zila Tolonium Chloride)
 - 1 Acetic Acid post-rinse solution swab, 1.3 mL (1% Acetic Acid)

Table A. Tolonium Chloride Staining Procedure

Type of Oral Illumination	Room Lighting	Solution	Volume	Contact Duration
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40-pack ViziLite Plus:

40 ViziLite acetic acid solution vials, 30 mL (1% Acetic Acid)

40 ViziLite lightsticks

40 ViziLite retractors

4 TBlue⁶³⁰ Oral Lesion Marking System kits each containing:

1 Acetic Acid pre-rinse solution swab, 1.3 mL (1% Acetic Acid)

1 Zila Tolonium Chloride solution swab, 1.3 mL (0.5% Zila Tolonium Chloride)

1 Acetic Acid post-rinse solution swab, 1.3 mL (1% Acetic Acid)

STORAGE:

Store between 15° and 25°C (59°F-77°F)

ViziLite, when used in combination with conventional visual oral mucosal examination by health care professionals, provides improved identification, evaluation, and monitoring of oral mucosal abnormalities in a population at increased risk for oral cancer.

The TBlue⁶³⁰ Oral Lesion Marking System can allow the examiner to continue to visualize white oral mucosal lesions using incandescent (conventional projected) light, even after the ViziLite and its holder are removed from the oral cavity. This allows the examiner to measure the lesion size, observe the lesion borders, and obtain an appropriate tissue sample (biopsy) when clinically indicated.

Caution: Federal law restricts this device to sale by or on the order of a dentist or physician.

Manufactured in the U.S.A. for:
Zila Pharmaceuticals, Inc.
Phoenix, AZ 85040

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