

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-dye 1% Acetic Acid solution swab to the stained lesion. Again, press firmly in a painting motion to apply the 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- or post-dye 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 musocal lesion(s); referring the patient to an appropriate specialist for further evaluation, etc.

Note: Care should be taken when applying TBlue as the dye will be retained on the vermilion border, dorsum of the tongue, (diffuse stain of the soft palate transferred from the dorsum of the tongue) and dental plaque. Acrylic restorations and appliances should be removed prior to application of TBlue. Common restorative materials including porcelain, composites, and acrylics and the margins of dental restorations may stain transiently; dental materials are not known to stain permanently.

HOW SUPPLIED

ViziLite TBlue Lesion Identification and Marking System is supplied with ViziLite Test Kits and TBlue Oral Lesion Marking System Kits in a 10-pack configuration, and a TBlue supplemental pack.

10-pack ViziLite TBlue

10 ViziLite Rinse Vials (1% Acetic Acid solution), 30mL

10 ViziLite lightsticks

10 ViziLite retractors

1 TBlue Oral Lesion Marking System kits, each containing: 1 1% Acetic Acid pre-dye solution swab, 1.3 ml
 1 TBlue solution swab, 1.3 ml (0.5% Zila Tolonium Chloride)
 1 1% Acetic Acid post-dye solution swab, 1.3 ml

TABLE 3

Tolonium Chloride Staining Procedure				
TYPE OF ORAL ILLUMINATION	ROOM LIGHTING	SOLUTION	VOLUME	CONTACT DURATION
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

ViziLite TBlue Supplemental Pack

1 ViziLite Rinse vial (1% Acetic Acid solution), 30 ml

1 ViziLite lightstick

1 ViziLite retractor

6 TBlue Oral Lesion Marking System kits, each containing:
 1 1% Acetic Acid pre-dye solution swab, 1.3 ml
 1 TBlue solution swab, 1.3 ml (0.5% Zila Tolonium Chloride)
 1 1% Acetic Acid post-dye solution swab, 1.3 ml

STORAGE

Store between 15° and 30°C (59°– 86°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.

TBlue 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. 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.



DEVICE DESCRIPTION

ViziLite TBlue Oral Lesion Identification and Marking System consists of ViziLite and TBlue® (Zila Tolonium Chloride) Oral Lesion Marking System. Following a conventional manual and visual oral examination, ViziLite is used for the identification, evaluation, and monitoring of oral mucosal abnormalities in a patient population at increased risk for oral cancer. TBlue Oral Lesion Marking System, is used to further assist with the evaluation and monitoring of lesions identified during the ViziLite exam.

ViziLite TBlue is a visualization system that is intended as an adjunct to conventional visual examination of the oral mucosa with incandescent light. ViziLite TBlue utilizes 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 stick, nor the ViziLite Rinse (1% Acetic Acid solution), have been changed for production of ViziLite TBlue.

TBlue Oral Lesion Marking System consists of three swab components: two swabs of 1% Acetic Acid solution, and one swab with TBlue solution, which is similar to the metachromatic vital dye known as toluidine blue.

TBlue Oral Lesion Marking System contains 1% Acetic Acid solution (with the inactive ingredients: Purified Water, USP; Sodium Benzoate, NF; and Natural 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; Dehydrated Alcohol, USP; and Natural Raspberry Flavor).

DEVICE ACCESSORY

ViziLite TBlue, as described above, may be used with or without ViziLite TBlue accessory eyewear, depending on the operatory environment. ViziLite TBlue accessory eyewear consists of lenses that filter ambient light outside the wavelength transmission range of the chemiluminescent light. Hence, there is no need to reduce or darken ambient lighting by extinguishing room light (other than patient light) or by other means (hood, drapes, or dedicated examination suite).

PRINCIPLE OF ACTION – VIZILITE

Following the application of a cytoplasmic dehydration agent such as an Acetic Acid solution, oral mucosal abnormalities 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 – predicate to OralLite Test Kit and ViziLite) a conventional projected incandescent light examination of the cervical squamous epithelium had been clinically shown to increase the detection of biopsy proven sqamous cell dysplasia (pre-malignant lesions) and malignancies 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 stained with TBlue, biopsied, then 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 current study examination, and there had been no change in the clinical appearance of the lesions.

Forty-five of the 92 lesions were determined to be atypical, i.e. mild dysplasia, moderate dysplasia, severe dysplasia (carcinoma-

TABLE 1

Biopsy Diagnoses of ViziLite Identified Lesions		
PATHOLOGY	DIAGNOSIS	QUANTITY
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

in-situ) or squamous cell carcinoma. The remaining 47 biopsies were considered not to have pathology. The correlations between the TBlue staining results and the biopsy results of the 92 lesions identified by ViziLite are presented in TABLE 2.

In TABLE 1, since all clinically suspicious lesions were biopsied, it can be seen that ViziLite identified all lesions containing any pathology with no false negatives (Sensitivity 100%).

In TABLE 2, 45 lesions were determined to be dysplastic on biopsy (exam positive or negative), the TBlue Oral Lesion Marking System identified 32 of them (71% Positive Predictive Value, PPV). It should be noted that all 10 cases of severe dysplasia (carcinoma-insitu) and all 8 cases of squamous cell cancer were ViziLite positive and TBlue positive (Negative Predictive Value, NPV of 100% for serious pathology).

The 13 ViziLite positive cases that were TBlue negative but biopsy positive consisted of 8 mildly dysplastic and 5 moderately dysplastic lesions.

INDICATIONS FOR USE

ViziLite TBlue Oral Lesion Identification and Marking System product consists of ViziLite and TBlue Oral Lesion Marking

TABLE 2

Correlation of Biopsy Results with the TBlue Examination Results			
TBLUE EXAM RESULT	MUCOSAL BIOPSY RESULTS (FOR ANY DYSPLASIA) OF VIZILITE POSITIVE LESIONS		
	Biopsy Positive	Biopsy Negative	Total
Positive	32	15	47
Negative	13	32	45
Total	45	47	

System and is intended to be used as an adjunct to the conventional manual and visual oral examination. The ViziLite (OralLite) is a chemiluminescent light stick indicated for use as an adjunct to conventional oral mucosal screening by trained health care providers for the identification, evaluation, and



BY ZILA

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

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monitoring of abnormalities in a patient population at increased risk for oral cancer. These include precancerous as well as cancerous lesions. ViziLite is also indicated for the identification of occult lesions not previously identified during conventional examination under incandescent illumination.

TBlue Oral Lesion Marking System is a three-component swab system which is indicated as an adjunct to the ViziLite examination for oral mucosa lesions for further evaluation and monitoring of lesions by physically marking lesions suspicious for cancer or precancer already differentially identified with ViziLite in a population at increased risk for oral cancer.

TBlue Oral Lesion Marking System is not being proposed for use in the initial oral mucosal examination without initial differential identification with ViziLite. The retention of the dye by a suspicious lesion may or may not indicate the need for further study, including biopsy.

CONTRAINDICATIONS

ViziLite TBlue Oral Lesion Identification and Marking System is contraindicated in patients with a known history of hypersensitivity to any of the ingredients or their analogs. TBlue Oral Lesion Marking System is contraindicated in patients who are pregnant or lactating.

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

TBlue 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 RINSE (1% ACETIC ACID SOLUTION)

Removable oral prostheses should be removed and any associated trauma or inflammation given time to heal prior to use of the product. Have the patient remove any acrylic-based prosthesis. In the event of an acrylic permanent crown, re-polish (if necessary) with standard prophylaxis paste and cup.

- Patients may experience a slight burning sensation of the oral mucosa due to the Acetic Acid.

- Do not swallow.

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

- Do not refrigerate ViziLite Rinse.

WARNING/PRECAUTIONS – VIZILITE

ViziLite is a single use device. Activated ViziLite should be firmly inserted into the provided ViziLite retractor before placing it into the patient’s mouth in order to prevent accidental swallowing or choking.

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

Inspect ViziLite for any evidence of chemical leakage prior to and after capsule activation in order to prevent potential leakage of ViziLite chemicals into the mouth. Discard any capsule that does not appear to be intact.

ViziLite lightsticks must be discarded in a proper receptacle.

Refer to the Material Safety Data Sheet (MSDS) for ViziLite TBlue in the case of accidental exposure.

WARNINGS/PRECAUTIONS – TBLUE ORAL LESION MARKING SYSTEM

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 TBlue procedure that there may be a residual bluish discoloration on the vermilion border, dorsum of the tongue, and dental plaque, which usually wears off in 2-6 hours. Staining in these areas with TBlue dye is normal and should not be considered a positive result in the absence of a clinically suspicious lesion.

Care should be taken to protect clothing, as well as equipment and environmental surfaces from being stained.

Should any of the material be accidentally swallowed, the urine and/or stools may be colored temporarily blue-green or blue, respectively. The patient should be advised of the possibility of this and assured that the color change is temporary.

Common restorative materials including porcelain, composites, and acrylics and margins of dental restorations may stain transiently; dental materials are not known to stain permanently.

INTERACTIONS

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

PREGNANCY AND LACTATION

TBlue 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.

TBlue Oral Lesion Marking System is contraindicated for lactating women. It is not known whether TBlue is excreted in human breast milk.

ADVERSE EVENTS

Patients may experience a slight burning sensation of the oral mucosa due to the Acetic Acid in the ViziLite Rinse and the TBlue Oral Lesion Marking System. No severe adverse reactions are expected when TBlue Oral Lesion Marking System is used according to package instructions. Some patients may find the taste of the product unappealing and may gag.

OVERDOSAGE

No adverse events have been reported in the published literature concerning the use of Tolonium Chloride, also known as toluidine blue, in the mouth for staining oral lesions. The TBlue Oral Lesion Marking System contains a 1.3 ml dye swab with 7 mg of Zila Tolonium Chloride, which conservatively yields an exposure of approximately 0.1 mg/kg (based on a 60 kg 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 tolonium chloride was 20 mg/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 TBLUE

The ViziLite examination consists of visualization of abnormal oral mucosal areas using a diffuse chemiluminescent light source. Following conventional manual and visual oral examination with incandescent light, there is a pre-exam rinse with ViziLite, activation of ViziLite, placement in the ViziLite retractor, dimming of ambient light and re-examination of the oral mucosa with ViziLite. Under ViziLite, atypical or dysplastic mucosal abnormalities may appear as bright white, distinctly demarcated, and sharply marginated areas that contrast with the surrounding non-involved epithelium. Any lesion identified with ViziLite may be further evaluated using the adjunctive TBlue Oral Lesion Marking System (pre- and post-dye 1% Acetic Acid solution swabs and TBlue stain swab). TBlue Oral Lesion Marking System should only be used in conjunction with a complete oral screening exam using the ViziLite.

This includes:

1. Conventional manual and visual oral examination with overhead exam light
2. A 30-60 second oral rinse with ViziLite 1% Acetic Acid solution
3. Examination with the ViziLite in a dim exam room or with ViziLite eyewear
4. Application of the pre-dye 1% Acetic Acid solution swab
5. Application of TBlue to any clinically suspicious mucosal abnormalities differentially identified with ViziLite
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 TBlue dye of a lesion seen with ViziLite should not preclude further analysis of the lesion, including biopsy. Any lesion seen by conventional or ViziLite examination may harbor pathology, and clinical judgment should always prevail when deciding the further analysis and management of these lesions.

ViziLite oral screening exam and, if indicated, application of TBlue Oral Lesion Marking System to any mucosal abnormalities should be done before the application of 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 TBlue Oral Lesion Marking System.

Instruments used in the mouth may cause minor abrasions that can retain the dye solution. In addition, areas of oral trauma (e.g. cheek bites) may be differentially identified of the ViziLite exam and may retain the dye solution. Before using TBlue 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.

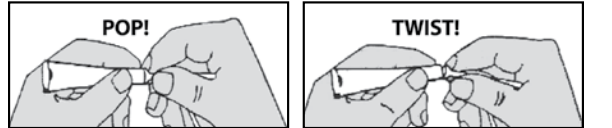
PROCEDURE FOR PERFORMING THE VIZILITE EXAM

1. Perform a conventional manual and visual examination of the oral cavity—note the presence of oral mucosal lesion(s).
2. Select ViziLite Pre-rinse solution (1% Acetic Acid rinse solution vial), one (1) ViziLite lightstick, and one (1) ViziLite retractor from the tray.
3. Instruct the patient to rinse their mouth with ViziLite Rinse in the 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, if not possible use ViziLite eye wear.
6. Repeat the exam of the oral cavity using illumination from the ViziLite.
7. Document oral mucosal lesion(s).
8. Remove ViziLite device from the mouth and discard.
9. Take appropriate clinical management action by either:
 - Documenting the absence of oral mucosal lesion(s)
 - Documenting the presence of oral mucosal lesion(s); and continue with the TBlue procedure

PROCEDURE FOR STAINING OF LESIONS IDENTIFIED BY VIZILITE WITH TBLUE ORAL LESION MARKING SYSTEM

1. After performing the conventional manual and visual examination of the oral cavity under incandescent illumination and performing the ViziLite oral examination, mucosal abnormalities differentially identified by the ViziLite and deemed clinically suspicious may be stained with TBlue 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 may TBlue Oral Lesion Marking System be used to demarcate the identified lesion(s) for further study, referral to a specialist or biopsy.
4. To open the swabs, pinch the tube firmly below the applicator handle.
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 ViziLite (if necessary), visualize the lesion(s). Apply swab #1, the pre-dye 1% Acetic Acid solution to the entire area of the previously identified lesions(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-dye solution.
8. Direct the patient to rinse and gargle with water and expectorate. This step may be repeated.
9. Lightly dry the area swabbed with the pre-dye solution with a gauze sponge or a gentle stream of air to minimize the risk of swallowing excess TBlue dye.
10. Continuing to use ViziLite illumination in a dim room (if necessary), apply swab #2, the TBlue swab (dye) to the suspicious 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. TBlue dye solution should be expectorated.