A patient's guide to treatment with VISUDYNE® (verteporfin for injection)

Indication

VISUDYNE® (verteporfin for injection) is used along with laser light treatment to stop leaking from blood vessels in the eye due to the following serious eye conditions: age-related macular degeneration (a condition affecting the retina of the eye which can impair vision), pathologic myopia (extreme nearsightedness) or ocular histoplasmosis (a certain type of fungus infection in the eye).

Please see Important Safety Information on Page 3 and accompanying full Prescribing Information.

BAUSCH + LOMB

Visudyne® verteporfin for injection

Contents

This brochure answers important questions about age-related macular degeneration (AMD) and provides important information on VISUDYNE® treatment—from how it works to what you should do before and after therapy. Some of the medical terminology used in this brochure may be unfamiliar. To help you to understand these medical terms, words that appear in boldface are defined in a glossary on page 11.

Indication

VISUDYNE® (verteporfin for injection) is used along with laser light treatment to stop leaking from blood vessels in the eye due to the following serious eye conditions: age-related macular degeneration (a condition affecting the retina of the eye which can impair vision), pathologic myopia (extreme nearsightedness) or ocular histoplasmosis (a certain type of fungus infection in the eye).

Important Safety Information

- VISUDYNE® (verteporfin for injection) should not be used if you have a condition known as porphyria, or if you are allergic to it or any of its components.
- Avoid exposure of skin and eyes to direct sunlight or bright indoor light for 5 days after treatment with VISUDYNE® by wearing protective clothes and dark sunglasses. A UV sunscreen will not offer enough protection for your skin. Wear a wristband to remind you to do this. However, do not stay in totally dark areas. You should expose your skin to regular indoor and/or indirect light because doing so will help inactivate the drug in your skin.
- In clinical studies, the most common side effects were injection site reactions (such as pain, redness, irritation, and swelling) or changes in vision (including blurred vision and flashes of light). Tell your doctor about any side effects that you may have.
- Do not drive or use machines if you develop or have changes in vision.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

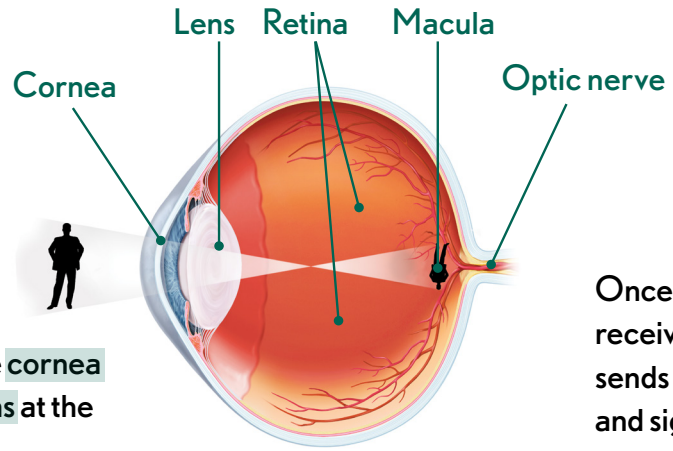
Please see accompanying Full Prescribing Information.

What is age-related macular degeneration?

Age-related macular degeneration (AMD) is a progressive eye disease that damages the **macula**. This part of the eye is responsible for central vision, which is needed to perform straight-ahead activities, such as reading, driving, or watching TV. A person diagnosed with AMD has either dry AMD or wet AMD.

AMD is not uncommon. In fact, AMD is a leading cause of severe vision loss in people over the age of 50. Many people may already have AMD without realizing it. Although wet AMD is far less common than the dry type, it is responsible for about 80% to 90% of severe vision loss related to AMD. That's why it's important to visit your eye doctor on a regular basis. It's the best defense to preserve your vision.

The parts of the eye and what they do



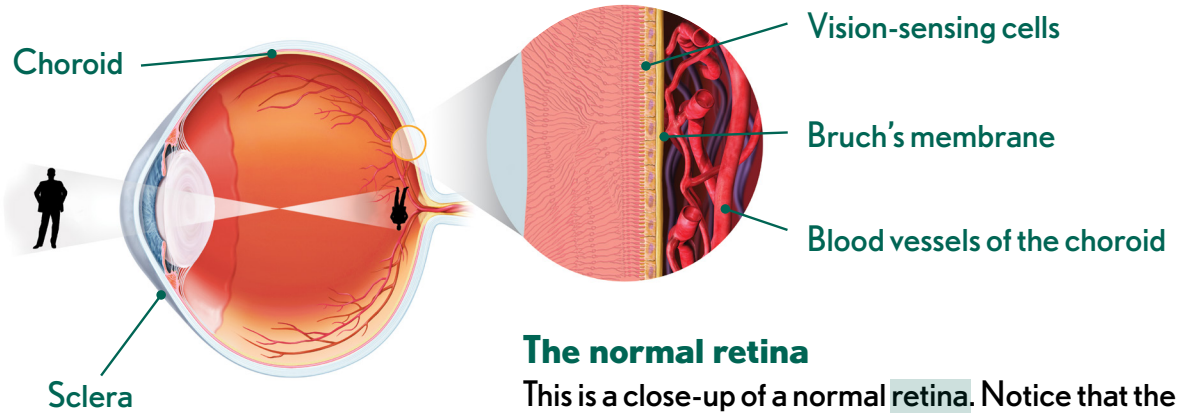
Light passes through the cornea and then through the lens at the front of the eye.

The light then travels to the back part of the eye, called the retina.

The light strikes the macula at the center of the retina, where vision is sharpest.

Once the retina and macula have received the light, the optic nerve sends a visual message to the brain, and sight is created.

What happens inside the eye?



The normal retina

This is a close-up of a normal retina. Notice that the yellow layer called Bruch's membrane separates blood vessels of the choroid from the rest of the retina.

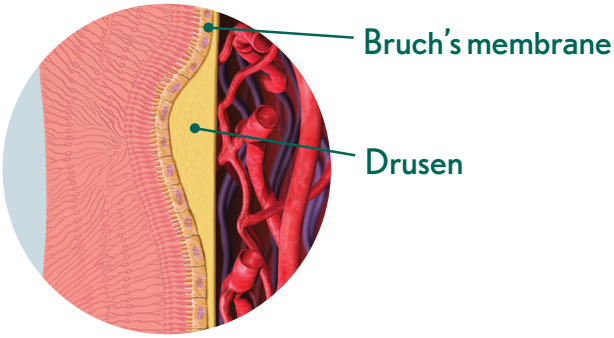
The eye is surrounded by a protective layer of fibrous tissue called the **sclera**. Deep in the back of the eye, tiny blood vessels supply blood to the **retina** and **macula**. The **macula** is located at the center of the **retina**. These blood vessels can be found in the **choroid**, a layer of the eye that lies between the **retina** and the **sclera**.

In wet AMD, when vision loss occurs, **drusen** (fatty deposits under the **macula**) and abnormal vessel growth are responsible. Abnormal vessel growth is also called choroidal neovascularization (CNV). Neo = new; vascularization = vessel growth.

What happens inside an eye with AMD?

Dry AMD

Fatty deposits called **drusen** accumulate in **Bruch's membrane**, which may negatively impact vision as they increase in size. VISUDYNE® is not approved to treat dry AMD.

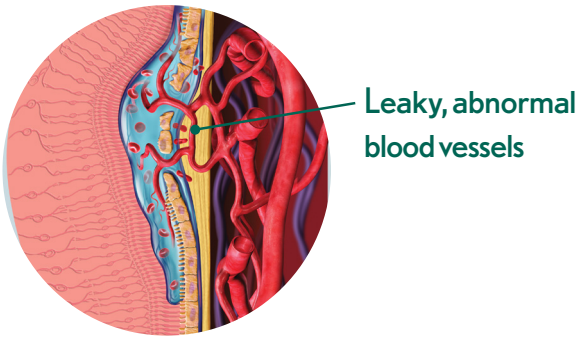


Wet AMD

Abnormal blood vessels push up into **Bruch's membrane**, leaking fluid and/or blood under the **macula** and causing serious vision loss.

A person with wet AMD may experience:

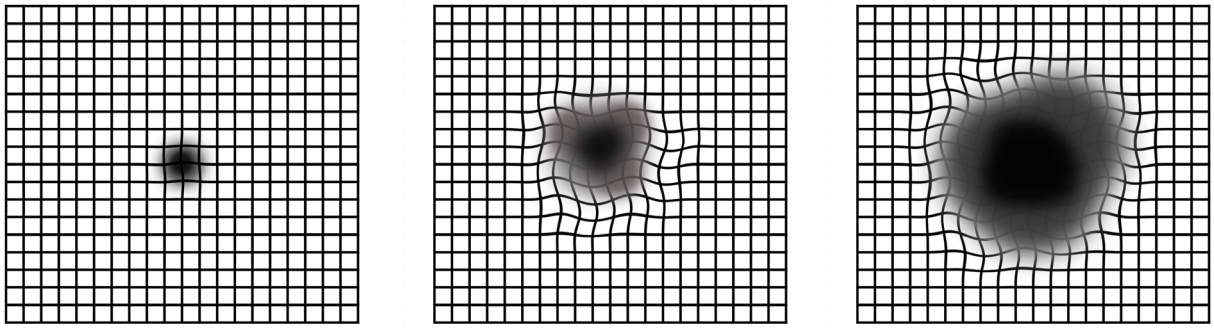
- Lines that appear wavy
- Blurring of faces
- Difficulty seeing colors
- Gaps in vision (i.e., dark or empty spaces that may block the center of vision)



How vision may change over time

When abnormal vessels leak fluid and/or blood under the **macula**, vision loss occurs because of damage and disruption to the retinal tissue. This damage often rapidly advances over time, affecting more of your vision. That is why it is so important for you to commit to a treatment plan with your eye care professional and stick to your regularly scheduled visits.

How changes might distort the appearance of an Amsler grid.*
An Amsler grid is a tool that lets you check changes in your vision.



What those changes may look like in everyday life.*

*The above are artists' representations and may not depict all patient situations.

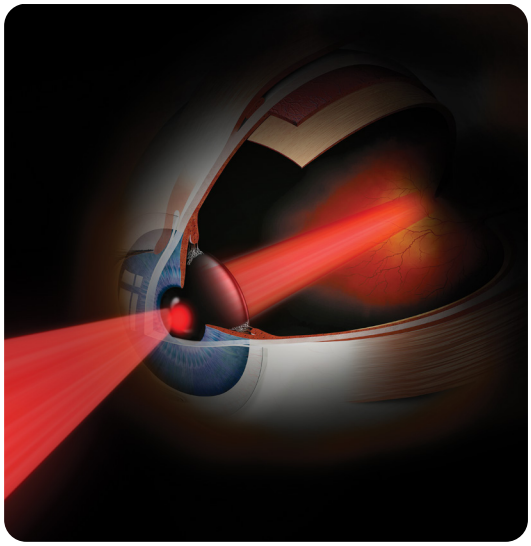
Why VISUDYNE® therapy may be right for you

VISUDYNE® therapy is approved to stop leaking from blood vessels in eyes that is caused by AMD (a condition affecting the retina of the eye which can impair vision). The sooner you begin therapy, the better your chances of retaining more of your vision.

Wet AMD is a serious eye disease that, if left untreated, can quickly cause severe vision loss. VISUDYNE® is a drug therapy that can slow the progression of wet AMD and may help you maintain your vision. Talk to your doctor about whether VISUDYNE® is right for you. Be sure to follow all of your doctor's instructions, as well as all recommended safety precautions.

How VISUDYNE® therapy works

VISUDYNE®, also known as verteporfin for injection, is a light-activated, or photodynamic, drug that is injected into the bloodstream and travels to the abnormal vessels. It is then activated by a low-energy laser, which produces a reaction that damages and closes abnormal vessels.



Multiple courses of therapy are often necessary because the abnormal blood vessels may not be fully closed off and leakage may recur. Despite the need for multiple treatments, stoppage of leakage and stability of visual function are achieved in many patients. VISUDYNE® therapy may be repeated at 3-month intervals if necessary.

VISUDYNE® is administered through an infusion into the patient's arm. The drug then circulates throughout the body; the abnormal vessels in the patient's eye attract and absorb the drug.

A low-energy laser is directed into the back of the eye at the abnormal vessels, activating the drug. The activated drug closes these abnormal vessels, most of which are thereby destroyed or sealed in such a way that they no longer leak.

Before you have VISUDYNE® therapy

Be sure to follow all of your doctor's instructions.
VISUDYNE® therapy causes your skin and eyes to become temporarily sensitive to light.
Bring these items with you on the day of your VISUDYNE® treatment appointment:

- **Dark sunglasses**
- A wide-brimmed hat
- Gloves
- Long pants
- A tight-weave, light-colored, long-sleeved shirt
- Socks and shoes

You should also make arrangements for someone to drive you home after your treatment.

During your treatment

1. You will receive an intravenous infusion of VISUDYNE®, usually in your arm, which should take about 10 minutes.
2. At the end of the infusion, your doctor will numb your eye with eye drops.
3. Fifteen minutes after the infusion begins, the doctor will place a special contact lens on your eye. A laser is then directed through the contact lens onto the affected area of the **retina** and applied for 83 seconds.
4. The laser activates the drug within the abnormal blood vessels to close the blood vessels and stop the leakage.

After you have VISUDYNE® therapy

Your skin will be sensitive to bright light and direct sunlight for 5 days after you have VISUDYNE® therapy. After 5 days, you may resume normal outdoor activities without any special precautions.

DO:

- Wear a wristband to remind yourself of your sensitivity
- Expose your skin to normal (fluorescent or incandescent) indoor light (this helps to inactivate the drug that may be present in your skin)
- Wait until sundown for outdoor activities if possible
- Be sure to wear protective clothing and sunglasses if you do go out during daylight hours in the first 5 days following therapy

DON'T:

- Stay in the dark indoors (normal indoor light helps to remove the drug from your skin)
- Visit your dentist or have surgery (lighting used in dentists' offices or surgical operating rooms can be dangerous as the drug may remain in your skin for several days)
- Go to tanning salons
- Use a pulse oxygen monitor

AVOID:

- Surgical procedures unless instructed by your doctor
- Unprotected skin and eye exposure to direct sunlight, skylights, undraped windows, and bright indoor light such as halogen lighting for the first 5 days after your treatment (wear protective clothing and sunglasses if you cannot avoid these situations; UV sunscreens are not effective in protecting against photosensitivity reactions)
- Driving or operating machinery if you develop visual disturbances such as blurred vision and other visual abnormalities

Be sure to follow all of your doctor's instructions.

What to expect at follow-up

Within 3 months, you should have another eye examination.

- Pictures will be taken of your eyes to show if any leakage is present
- VISUDYNE® therapy usually consists of a series of sessions. If the pictures show that there is more leakage, additional therapy will be necessary

Retreatment with VISUDYNE® therapy

More than one treatment with VISUDYNE® may be necessary to fully address the issues of wet AMD. In clinical studies, the need for retreatment steadily declined over time. Please note that the efficacy and safety of VISUDYNE® in clinical studies have not been demonstrated beyond 2 years.

What can you do about vision you've already lost?

- Visit your eye care professional on a regular basis to explore all of your treatment options
- Ask your eye care professional about low vision services and devices that may help you make the most of your remaining vision. Ask for a referral to a specialist in low vision
- Many organizations offer information about low vision counseling, training, and other special services. Some of those are listed in this brochure

Glossary

Bruch's membrane: A thin layer of tissue that separates the pigmented layer of the retina from the choroid layer

Choroid: Layer of the eye that is made up of tiny blood vessels, which lies between the retina and the sclera. The dark-colored pigment in the choroid absorbs light and limits reflections within the eye that could affect vision

Cornea: The clear front window of the eye that allows light to enter the eyeball

Drusen: Tiny yellow or white fatty deposits in the retina

Lens: Transparent body located behind the cornea that focuses the incoming light rays onto the retina

Macula: A small spot of light-sensitive cells located at the center of the retina. The macula is specifically responsible for central vision

Optic nerve: The nerve that carries visual signals from the retina to the brain

Retina: Light-sensitive nerve layer that lines the back of the eye. The retina receives visual images from the lens and transmits them to the optic nerve

Sclera: The protective layer of fibrous tissue that surrounds the entire eyeball, except the cornea

Where can you find more information about AMD?

Foundation Fighting Blindness
7168 Columbia Gateway Drive, Suite 100
Columbia, MD 21046
Phone: 1-800-683-5555
Web address: www.blindness.org

Macular Degeneration Support
3600 Blue Ridge Blvd
Grandview, MO 64030
Phone: 1-888-866-6148
1-816-761-7080
Web address: www.mdsupport.org

National Alliance for Eye and Vision Research
1801 Rockville Pike, Suite 400
Rockville, MD 20852
Phone: 1-240-221-2905
Web address: www.eyeresearch.org

Prevent Blindness America
225 West Wacker Drive, Suite 400
Chicago, IL 60606
Phone: 1-800-331-2020
Web address: www.preventblindness.org

The Seniors Coalition
1250 Connecticut Avenue, NW, Suite 200
Washington, DC 20036
Phone: 1-202-261-3594
Web address: www.senior.org

Low vision services and programs

American Foundation for the Blind
1401 South Clark Street, Suite 730
Arlington, VA 22202
Phone: 1-212-502-7600
Web address: www.afb.org

Lighthouse Guild
The Sol and Lillian Goldman Building
250 West 64th Street
New York, NY 10023
Phone: 1-800-284-4422
1-212-821-9200
1-212-821-9713 (TTY)
Web address: www.lighthouse.org

References: 1. VISUDYNE [package insert], 2017. **2**. Kaiser PK; Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: 5-year results of two randomized clinical trials with an open-label extension. TAP report no. 8. *Graefes Arch Clin Exp Ophthalmol.* 2006;244(9):1132-1142.

Visudyne® verteporfin for injection
www.VISUDYNE.com

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VISUDYNE safely and effectively. See full prescribing information for VISUDYNE.

VISUDYNE® (verteporfin for injection), for intravenous use
Initial U.S. Approval: 2000

---------- INDICATIONS AND USAGE ----------

VISUDYNE therapy is indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Reconstitute each vial of VISUDYNE with 7 mL of Sterile Water for Injection to provide 7.5 mL containing 2 mg/mL. Reconstituted VISUDYNE must be protected from light and used within 4 hours. (2.3)
- The recommended light dose is 50 J/cm^2 of neovascular lesion administered at an intensity of 600 mW/cm^2. The wavelength of the laser light should be 689±3 nm. This light dose is administered over 83 seconds, starting 15 minutes after the start of the VISUDYNE infusion. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

- VISUDYNE is a reconstituted sterile solution intended for intravenous injection. (3)
- Each reconstituted vial provides 7.5 mL solution containing 2 mg/mL of verteporfin. (3)

---------- CONTRAINDICATIONS ----------

VISUDYNE is contraindicated for patients with porphyria or a known hypersensitivity to any component of this preparation. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Extravasation: If extravasation occurs, the infusion should be stopped immediately. The extravasation area must be thoroughly protected from direct light until swelling and discoloration have faded in order to prevent the occurrence of local burn. (5.1)
- Following injection with VISUDYNE, care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days. (5.2)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence >10%) are:

- injection site reactions (6.1)
- visual disturbances (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC, at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VISUDYNE (verteporfin for injection) therapy is indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD), pathologic myopia or presumed ocular histoplasmosis.

There is insufficient evidence to indicate VISUDYNE for the treatment of predominantly occult subfoveal CNV.

2 DOSAGE AND ADMINISTRATION

A course of VISUDYNE therapy is a two-step process requiring administration of both drug and light.

The first step is the intravenous infusion of VISUDYNE. The second step is the activation of VISUDYNE with light from a nonthermal diode laser.

The physician should re-evaluate the patient 3 months after treatment and if choroidal neovascular leakage is detected on fluorescein angiography, therapy may be repeated.

2.1 Lesion Size Determination

The greatest linear dimension (GLD) of the lesion should be estimated by fluorescein angiography and color fundus photography. All classic and occult CNV, blood and/or blocked fluorescence, and any serous detachments of the retinal pigment epithelium should be included for this measurement. Fundus cameras with magnification within the range of 2.4-2.6X are recommended. The GLD of the lesion on the fluorescein angiogram must be corrected for the magnification of the fundus camera to obtain the GLD of the lesion on the retina.

2.2 Spot Size Determination

The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow a 500 micron border, ensuring full coverage of the lesion. The maximum spot size used in the clinical trials was 6400 microns.

The nasal edge of the treatment spot must be positioned at least 200 microns from the temporal edge of the optic disc, even if this will result in lack of photoactivation of CNV within 200 microns of the optic nerve.

2.3 VISUDYNE Administration

Reconstitute each vial of VISUDYNE with 7 mL of Sterile Water for Injection to provide 7.5 mL containing 2 mg/mL of verteporfin. Reconstituted VISUDYNE must be protected from light and used within 4 hours. It is recommended that reconstituted VISUDYNE be inspected visually for particulate matter and discoloration prior to administration. Reconstituted VISUDYNE is an opaque dark green solution. VISUDYNE may precipitate in saline solutions. Do not use normal saline or other parenteral solutions, except 5% Dextrose for Injection, for dilution of the reconstituted VISUDYNE. Do not mix VISUDYNE in the same solution with other drugs.

The volume of reconstituted VISUDYNE required to achieve the desired dose of 6 mg/m^2 body surface area is withdrawn from the vial and diluted with 5% Dextrose for Injection to a total infusion volume of 30 mL. After dilution, protect from light and use within 4 hours. The full infusion volume is administered intravenously over 10 minutes at a rate of 3 mL/minute, using an appropriate syringe pump and in-line filter. The clinical studies were conducted using a standard infusion line filter of 1.2 microns.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, protect the site from light *[see Warnings and Precautions (5.1)]*.

2.4 Light Administration

Initiate 689 nm wavelength laser light delivery to the patient 15 minutes after the start of the 10 minute infusion with VISUDYNE.

Photoactivation of VISUDYNE is controlled by the total light dose delivered. In the treatment of CNV, the recommended light dose is 50 J/cm^2 of neovascular lesion administered at an intensity of 600 mW/cm^2. This dose is administered over 83 seconds.

Light dose, light intensity, ophthalmic lens magnification factor and zoom lens setting are important parameters for the appropriate delivery of light to the predetermined treatment spot. Follow the laser system manuals for procedure set up and operations.

The laser system must deliver a stable power output at a wavelength of 689±3 nm. Light is delivered to the retina as a single circular spot via a fiber optic and a slit lamp, using a suitable ophthalmic magnification lens.

The following laser systems have been tested for compatibility with VISUDYNE and are approved for delivery of a stable power output at a wavelength of 689±3 nm:

Coherent Opal Photoactivator laser console and modified Coherent LaserLink adapter, manufactured by Lumenis, Inc., 2400 Condensa Street, Santa Clara, CA 95051-0901,

Zeiss VISULAS 690s laser and VISULINK PDT adapter manufactured by Carl Zeiss Meditec Inc., 5160 Hacienda Drive, Dublin, CA 94568,

Ceralas I laser system and Ceralink Slit Lamp Adapter manufactured by Biolitec Inc., 515 Shaker Road, East Longmeadow, MA 01028,

Quantel Activis laser console and the ZSL30 ACT, ZSL120 ACT and HSBMBQ ACT slit lamp adapters distributed by Quantel Medical, 601 Haggerty Lane, Bozeman, MT 59715

2.5 Concurrent Bilateral Treatment

The controlled trials only allowed treatment of one eye per patient. In patients who present with eligible lesions in both eyes, physicians should evaluate the potential benefits and risks of treating both eyes concurrently. If the patient has already received previous VISUDYNE therapy in one eye with an acceptable safety profile, both eyes can be treated concurrently after a single administration of VISUDYNE. The more aggressive lesion should be treated first, at 15 minutes after the start of infusion. Immediately at the end of light application to the first eye, the laser settings should be adjusted to introduce the treatment parameters for the second eye, with the same light dose and intensity as for the first eye, starting no later than 20 minutes from the start of infusion.

In patients who present for the first time with eligible lesions in both eyes without prior VISUDYNE therapy, it is prudent to treat only one eye (the most aggressive lesion) at the first course. One week after the first course, if no significant safety issues are identified, the second eye can be treated using the same treatment regimen after a second VISUDYNE infusion. Approximately 3 months later, both eyes can be evaluated and concurrent treatment following a new VISUDYNE infusion can be started if both lesions still show evidence of leakage.

3 DOSAGE FORMS AND STRENGTHS

VISUDYNE is a reconstituted sterile solution intended for intravenous injection only. Each reconstituted vial provides 7.5 mL solution containing 2 mg/mL of verteporfin.

4 CONTRAINDICATIONS

VISUDYNE is contraindicated for patients with porphyria or a known hypersensitivity to any component of this preparation *[see Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Local Adverse Reactions - Extravasation

Standard precautions should be taken during infusion of VISUDYNE to avoid extravasation. Examples of standard precautions include, but are not limited to:

- A free-flowing intravenous (IV) line should be established before starting VISUDYNE infusion and the line should be carefully monitored.
- Due to the possible fragility of vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably antecubital, be used for injection.
- Small veins in the back of the hand should be avoided.

Extravasation of VISUDYNE, especially if the affected area is exposed to light, can cause severe pain, inflammation, swelling or discoloration at the injection site.

If extravasation does occur, the infusion should be stopped immediately. The extravasation area must be thoroughly protected from direct light until swelling and discoloration have faded in order to prevent the occurrence of local burn, which could be severe. Cold compresses should be applied to the injection site. Oral medications for pain relief may be administered.

5.2 Exposure to Sun or Direct Light

Following injection with VISUDYNE, care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days. In the event of extravasation during infusion, the extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

5.3 Decreased Vision After Treatment

Patients who experience severe decrease of vision of 4 lines or more within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Local Adverse Reactions – Extravasation *[see Warnings and Precautions (5.1)]*
- Exposure to Sun or Direct Light *[see Warnings and Precautions (5.2)]*
- Decreased Vision After Treatment *[see Warnings and Precautions (5.3)]*
- Porphyria and Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

Severe chest pain, vasovagal and hypersensitivity reactions have been reported. Vasovagal and hypersensitivity reactions on rare occasions can be severe. These reactions may include syncope, sweating, dizziness, rash, dyspnea, flushing and changes in blood pressure and heart rate. General symptoms can include headache, malaise, urticaria, and pruritus.

The most frequently reported adverse reactions to VISUDYNE are injection site reactions (including pain, edema, inflammation, extravasation, rashes, hemorrhage and discoloration) and visual disturbances (including blurred vision, flashes of light, decreased visual acuity and visual field defects, including scotoma). These events occurred in approximately 10%-30% of patients. The following events, listed by Body System, were reported more frequently with VISUDYNE therapy than with placebo therapy and occurred in 1%-10% of patients:

Ocular Treatment Site:	Blepharitis, cataracts, conjunctivitis/conjunctival infection, dry eyes, ocular itching, severe vision decrease with or without subretinal/retinal or vitreous hemorrhage
Body as a Whole:	Asthenia, fever, flu syndrome, infusion related pain primarily presenting as back pain, photosensitivity reactions
Cardiovascular:	Atrial fibrillation, hypertension, peripheral vascular disorder, varicose veins
Dermatologic:	Eczema
Digestive:	Constipation, gastrointestinal cancers, nausea
Hemic and Lymphatic:	Anemia, white blood cell count decreased, white blood cell count increased
Hepatic:	Elevated liver function tests
Metabolic/Nutritional:	Albuminuria, creatinine increased
Musculoskeletal:	Arthralgia, arthrosis, myasthenia
Nervous System:	Hypesthesia, sleep disorder, vertigo
Respiratory:	Cough, pharyngitis, pneumonia
Special Senses:	Cataracts, decreased hearing, diplopia, lacrimation disorder
Urogenital:	Prostatic disorder

Severe vision decrease, equivalent of >4 lines, within 7 days after treatment has been reported in 1%-5% of patients. Partial recovery of vision was observed in some patients. Photosensitivity reactions usually occurred in the form of skin sunburn following exposure to sunlight. The higher incidence of back pain in the VISUDYNE group occurred primarily during infusion.

The following adverse events have occurred either at low incidence (<1%) during clinical trials or have been reported during the use of VISUDYNE in clinical practice where these reactions were reported voluntarily from a population of unknown size and frequency of occurrence cannot be determined precisely. They have been chosen for inclusion based on factors such as seriousness, frequency of reporting, possible causal connection to VISUDYNE, or a combination of these factors:

Ocular Treatment Site:	Retinal detachment (nonrhegmatogenous), retinal or choroidal vessel nonperfusion, retinal pigment epithelial tear.
Non-ocular Events:	Chest pain and other musculoskeletal pain during infusion

7 DRUG INTERACTIONS

Drug interaction studies in humans have not been conducted with VISUDYNE.

Verteporfin is rapidly eliminated by the liver, mainly as unchanged drug. Metabolism is limited and occurs by liver and plasma esterases. Microsomal cytochrome P450 does not appear to play a role in verteporfin metabolism.

Based on the mechanism of action of verteporfin, many drugs used concomitantly could influence the effect of VISUDYNE therapy. Possible examples include the following:

Calcium channel blockers, polymyxin B or radiation therapy could enhance the rate of VISUDYNE uptake by the vascular endothelium. Other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics and griseofulvin) could increase the potential for skin photosensitivity reactions. Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, β-carotene, ethanol, formate and mannitol, would be expected to decrease VISUDYNE activity. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could also decrease the efficacy of VISUDYNE therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with the use of VISUDYNE in pregnant women to inform a drug-associated risk. Intravenous administration of verteporfin to pregnant rats during the period of organogenesis produced an increase in the incidence of anophthalmia/microphthalmia and wavy ribs at exposures approximately 40-fold the human exposure at the recommended clinical dose.

Verteporfin did not produce adverse fetal effect in rats or rabbits at exposures 6 -to 20-fold the human exposure at the recommended clinical dose.

There are no adequate and well-controlled studies in pregnant women. VISUDYNE should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

Rat fetuses of dams administered verteporfin for injection intravenously during organogenesis exhibited an increase in the incidence of anophthalmia/microphthalmia and wavy ribs at doses ≥10 mg/kg/day (approximately 40-fold the human exposure at the recommended dose of 6 mg/m^2, based on AUC in female rats). No teratogenic effects were observed in rat fetuses at a dose of 2 mg/kg/day (approximately 6-fold the human exposure at the recommended dose of 6 mg/m^2, based on AUC in female rats).

In pregnant rabbits, a decrease in maternal body weight gain and food consumption was observed in animals that received verteporfin for injection intravenously at doses up to 10 mg/kg/day during organogenesis. The no observed adverse effect level (NOAEL) for maternal toxicity was 3 mg/kg/day (approximately 6-fold the recommended human dose of 6 mg/m^2, based on body surface area). No teratogenic effects were observed in rabbit

fetuses at doses up to 10 mg/kg/day (approximately 20-fold the recommended human dose of 6 mg/m^2, based on body surface area).

8.2 Lactation

Risk Summary

Verteporfin and its diacid metabolite have been found in human breast milk following an intravenous infusion at the recommended human dose of 6 mg/m^2. Verteporfin was present in breast milk at levels up to 66% of the corresponding plasma levels and declined below the limit of quantification (2 ng/mL) within 24 hours. The diacid metabolite had lower peak concentrations but persisted up to at least 48 hours.

Because of the potential for serious adverse reactions in nursing infants from VISUDYNE, a decision should be made whether to discontinue nursing or postpone treatment, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

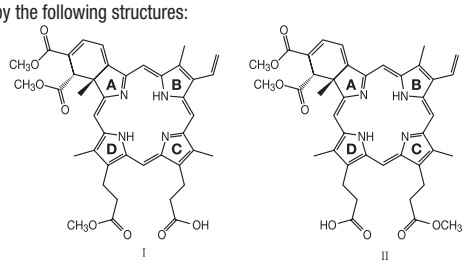
Approximately 90% of the patients treated with VISUDYNE in the clinical efficacy trials were over the age of 65. A reduced treatment effect was seen with increasing age.

10 OVERDOSAGE

Overdose of drug and/or light in the treated eye may result in non-perfusion of normal retinal vessels with the possibility of severe decrease in vision that could be permanent. An overdose of drug will also result in the prolongation of the period during which the patient remains photosensitive to bright light. In such cases, it is recommended to extend the photosensitivity precautions for a time proportional to the overdose.

11 DESCRIPTION

VISUDYNE is a light activated drug used in photodynamic therapy. The finished drug product is a lyophilized dark green cake. Verteporfin is a 1:1 mixture of two regioisomers (I and II), represented by the following structures:



I II

The chemical names for the verteporfin regioisomers are:

9-methyl (I) and 13-methyl (II) trans-(±)-18-ethenyl-4,4a,-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H, 25H-benzo[b]porphine-9,13-dipropanoate

The molecular formula is $C_{41}H_{42}N_4O_8$ with a molecular weight of approximately 718.8. Each mL of reconstituted VISUDYNE contains:

ACTIVE:	Verteporfin, 2 mg
INACTIVES:	Ascorbyl palmitate, butylated hydroxytoluene, dimyristoyl phosphatidylcholine, egg phosphatidylglycerol and lactose

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VISUDYNE therapy is a two-stage process requiring administration of both verteporfin for injection and nonthermal red light.

Verteporfin is transported in the plasma primarily by lipoproteins. Once verteporfin is activated by light in the presence of oxygen, highly reactive, short-lived singlet oxygen and reactive oxygen radicals are generated. Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion. Damaged endothelium is known to release procoagulant and vasoactive factors through the lipoxygenase (leukotriene) and cyclo-oxygenase (eicosanoids such as thromboxane) pathways, resulting in platelet aggregation, fibrin clot formation and vasoconstriction. Verteporfin appears to somewhat preferentially accumulate in neovasculature, including choroidal neovasculature. However, animal models indicate that the drug is also present in the retina. Therefore, there may be collateral damage to retinal structures following photoactivation including the retinal pigmented epithelium and outer nuclear layer of the retina. The temporary occlusion of the CNV following VISUDYNE therapy has been confirmed in humans by fluorescein angiography.

12.3 Pharmacokinetics

Following intravenous infusion, verteporfin exhibits a bi-exponential elimination with a terminal elimination half-life of approximately 5-6 hours. The extent of exposure and the maximal plasma concentration are proportional to the dose between 6 and 20 mg/m^2. At the intended dose, pharmacokinetic parameters are not significantly affected by gender.

Verteporfin is metabolized to a small extent to its diacid metabolite by liver and plasma esterases. NADPH-dependent liver enzyme systems (including the cytochrome P450 isozymes) do not appear to play a role in the metabolism of verteporfin. Elimination is by the fecal route, with less than 0.01% of the dose recovered in urine.

In a study of patients with mild hepatic insufficiency (defined as having two abnormal hepatic function tests at enrollment), AUC and C_{max} were not significantly different from the control group; half-life, however, was significantly increased by approximately 20%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No studies have been conducted to determine the carcinogenic potential of verteporfin.

Mutagenesis

Photodynamic therapy (PDT) as a class has been reported to result in DNA damage including DNA-strand breaks, alkali-labile sites, DNA degradation, and DNA-protein cross-links which may result in chromosomal aberrations, sister chromatid exchanges (SCE), and mutations. In addition, other photodynamic therapeutic agents have been shown to increase the incidence of SCE in Chinese hamster ovary (CHO) cells irradiated with visible light and in Chinese hamster lung fibroblasts irradiated with near UV light, increase mutations and DNA-protein cross-linking in mouse L5178 cells, and increase DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. Verteporfin was not evaluated in these latter systems. It is not known how the potential for DNA damage with PDT agents translates into human risk.

Impairment of Fertility

No effect on male or female fertility has been observed in rats following intravenous administration of verteporfin for injection up to 10 mg/kg/day (approximately 60- and 40-fold human exposure at 6 mg/m^2 based on AUC in male and female rats, respectively).

13.2 Animal Toxicology and/or Pharmacology

At a >10-fold higher dose given by bolus injection to sedated or anesthetized pigs, verteporfin caused severe hemodynamic effects, including death, probably as a result of complement activation. These effects were diminished or abolished by pretreatment with antihistamine and they were not seen in conscious nonsedated pigs.

14 CLINICAL STUDIES

14.1 Age-Related Macular Degeneration (AMD)

Two adequate and well-controlled, double-masked, placebo-controlled, randomized studies were conducted in patients with classic-containing subfoveal CNV secondary to AMD. A total of 609 patients (VISUDYNE 402, placebo 207) were enrolled in these two studies. During these studies, retreatment was allowed every 3 months if fluorescein angiograms showed any recurrence or persistence of leakage. The placebo control (sham treatment) consisted of intravenous administration of Dextrose 5% in Water, followed by light application identical to that used for VISUDYNE therapy.

The difference between treatment groups statistically favored VISUDYNE at the 1-year and 2-year analyses for visual acuity endpoints.

The subgroup of patients with predominately classic CNV lesions was more likely to exhibit a treatment benefit (N=242; VISUDYNE 159, placebo 83).

Predominantly classic CNV lesions were defined as those in which the classic component comprised 50% or more of the area of the entire lesion. For the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity), these patients showed a difference of approximately 28% between treatment groups at both Months 12 and 24 (67% for VISUDYNE patients compared to 40% for placebo patients, at Month 12; and 59% for VISUDYNE patients compared to 31% for placebo patients, at Month 24). Severe vision loss (≥6 lines of visual acuity from baseline) was experienced by 12% of VISUDYNE-treated patients compared to 34% of placebo-treated patients at Month 12, and by 15% of VISUDYNE-treated patients compared to 36% of placebo-treated patients at Month 24.

Patients with predominantly classic CNV lesions that did not contain occult CNV exhibited the greatest benefit (N=134; VISUDYNE 90, placebo 44). At 1 year, these patients demonstrated a 49% difference between treatment groups when assessed by the <3 lines-lost definition (77% vs. 27%).

Older patients (≥75 years), patients with dark irides, patients with occult lesions or patients with less than 50% classic CNV were less likely to benefit from VISUDYNE therapy.

The safety and efficacy of VISUDYNE beyond 2 years have not been demonstrated.

Based on the Treatment of Age Related Macular Degeneration with Photodynamic Therapy Study (TAP) extension study, the average number of treatments per year were 3.5 in the first year after diagnosis, 2.4 in the second, 1.3 in the third, 0.4 in the fourth and 0.1 in the fifth year.

14.2 Pathologic Myopia

One adequate and well-controlled, double-masked, placebo-controlled, randomized study was conducted in patients with subfoveal CNV secondary to pathologic myopia. A total of 120 patients (VISUDYNE 81, placebo 39) were enrolled in the study. The treatment dosing and retreatments were the same as in the AMD studies. The difference between treatment groups statistically favored VISUDYNE at the 1-year analysis but not at the 2-year analysis for visual acuity endpoints. For the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity), patients at the 1-year timepoint showed a difference of approximately 19% between treatment groups (86% for VISUDYNE patients compared to 67% for placebo patients). However, by the 2-year timepoint, the effect was no longer statistically significant (79% for VISUDYNE patients compared to 72% for placebo patients).

Based on the Verteporfin in Photodynamic Therapy in Pathologic Myopia (VIP-PM) extension study in pathologic myopia, the average number of treatments per year were 3.5 in the first year after diagnosis, 1.8 in the second, 0.4 in the third, 0.2 in the fourth and 0.1 in the fifth.

14.3 Presumed Ocular Histoplasmosis

One open-label study was conducted in patients with subfoveal CNV secondary to presumed ocular histoplasmosis. A total of 26 patients were treated with VISUDYNE in the study. The treatment dosing and retreatments for VISUDYNE were the same as the AMD studies. VISUDYNE-treated patients compare favorably with historical control data demonstrating a reduction in the number of episodes of severe visual acuity loss (>6 lines of loss).

Based on the Visudyne Ocular Histoplasmosis extension study in presumed ocular histoplasmosis, the average number of treatments per year was 2.9 in the first year after diagnosis, 1.2 in the second, 0.2 in the third and 0.1 in the fourth.

16 HOW SUPPLIED/STORAGE AND HANDLING

VISUDYNE (verteporfin for injection) is supplied in a single-use glass vial with a gray bromobutyl stopper and aluminum flip-off cap. It contains a lyophilized dark green cake with 15 mg verteporfin.

NDC 0187-5600-15

Store VISUDYNE between 20°-25°C (68°-77°F).

16.1 Spills and Disposal

Spills of VISUDYNE should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light. Use of rubber gloves and eye protection is recommended. All materials should be disposed of properly.

16.2 Accidental Exposure

Because of the potential to induce photosensitivity reactions, it is important to avoid contact with the eyes and skin during preparation and administration of VISUDYNE. Any exposed person must be protected from bright light *[see Warnings and Precautions (5.2)]*.

17 PATIENT COUNSELING INFORMATION

Advise patients who receive VISUDYNE that they will become temporarily photosensitive after the infusion. Patients should be advised to wear a wrist band to remind them to avoid direct sunlight for 5 days. During that period, patients should be advised to avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light. Sources of bright light include, but are not limited to, tanning salons, bright halogen lighting and high power lighting used in surgical operating rooms or dental offices. Prolonged exposure to light from light-emitting medical devices such as pulse oximeters should also be avoided for 5 days following VISUDYNE administration.

If treated patients must go outdoors in daylight during the first 5 days after treatment, they should be advised to protect all parts of their skin and their eyes by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions because photoactivation of the residual drug in the skin can be caused by visible light. Patients should be advised to not stay in the dark and should be encouraged to expose their skin to ambient indoor light, as it will help inactivate the drug in the skin through a process called photobleaching.

Following VISUDYNE treatment, patients should be advised that they may develop visual disturbances such as abnormal vision, vision decrease, or visual field defects that may interfere with their ability to drive or use machines. Patients should be advised to not drive or use machines as long as these symptoms persist.

Manufactured for:
Bausch + Lomb, a division of
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Manufactured by:
Alcami Carolinas Corporation
Charleston, SC 29405 USA

REF-VID-0188