The greatest linear dimension (GLD) of the lesion should be estimated by fluorescein angiography and the treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow treatment of the entire lesion. The treatment spot should be placed at least 1000 microns lateral and 1000 microns above and below the center of the lesion. The treatment spot should be placed on the foveal avascular zone only if the lesion is large enough to extend to the foveal avascular zone. The treatment spot must cross the lesion boundary at least once. The treatment spot must not overlap any normal adjacent retina.

The first step is the intravenous infusion of VISUDYNE. The second step is the activation of VISUDYNE with laser energy. The latter must be administered over 83 seconds. The laser systems tested for compatibility with VISUDYNE are Quantel Activis laser console and the ZSL30 ACT, ZSL120 ACT and HSBMBQ ACT slit lamp laser systems. The Zeiss VISULAS 690s laser and VISULINK PDT adapter manufactured by Carl Zeiss Meditec Inc., North Chesterfield, VA is also approved. These laser systems will be used with a spot size of approximately 1000 microns in diameter. If the lesion is non-foveal, the spot size should be adjusted to encompass the lesion.

The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow treatment of the entire lesion. The treatment spot should be placed at least 1000 microns lateral and 1000 microns above and below the center of the lesion. The treatment spot should be placed on the foveal avascular zone only if the lesion is large enough to extend to the foveal avascular zone. The treatment spot must cross the lesion boundary at least once. The treatment spot must not overlap any normal adjacent retina.

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The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow treatment of the entire lesion. The treatment spot should be placed at least 1000 microns lateral and 1000 microns above and below the center of the lesion. The treatment spot should be placed on the foveal avascular zone only if the lesion is large enough to extend to the foveal avascular zone. The treatment spot must cross the lesion boundary at least once. The treatment spot must not overlap any normal adjacent retina.

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The following adverse events have occurred either at least twice in >1% of patients in clinical studies or at twice the incidence of control subjects in the pharmacokinetics studies on which the dosing regimen is based: headache, nausea, myalgia, fatigue, constipation, diarrhea, pruritus, skin discoloration, flushing, rash, injection site reactions, dizziness, taste perversion, back pain, injection site pain, hypertension, hypotension, rash, pruritus, flushing, injection site swelling, phlebitis, injection site hemorrhage, injection site reaction, injection site pain, injection site edema, urticaria, and injection site induration.

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

12.3 Pharmacokinetics
Verteporfin is rapidly metabolized by the liver, mainly as unchanged drug. Metabolites are limited and could not be identified by HPLC analysis. They have been characterized by HPLC analysis in extracts from rat, rabbit, and monkey tissue as well as in human postmortem tissue.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of fertility
No studies have been done to determine the carcinogenic potential of verteporfin.

Pharmacology
Pharmacokinetics (PD): VISUDYNE is absorbed following IV administration and has a rapid plasma clearance. Visudyne is distributed to all tissues and organs. Following IV administration, free verteporfin concentration is higher in the skin and skin appendages as compared with other tissues. By 5 days following VISUDYNE administration, tissue levels of verteporfin and its diacid metabolite are undetectable. Plasma concentrations of verteporfin and its diacid metabolite are reduced by approximately 90% following a single IV dose and by approximately 99% following a course of therapy. Reduced plasma levels were associated with a decrease in tissue and tissue deposition of verteporfin and its diacid metabolite.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
There are no adequate and well-controlled studies in pregnant women. Visudyne should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Lactation
Breast milk levels of verteporfin were not measured in women who were exposed to VISUDYNE during breast feeding. Based on animal data, VISUDYNE treatment should be avoided during breast feeding.

8.3 Pediatric Use
Verteporfin is rapidly eliminated by the liver, mainly as unchanged drug. Metabolites are limited and could not be identified by HPLC analysis. They have been characterized by HPLC analysis in extracts from rat, rabbit, and monkey tissue as well as in human postmortem tissue.

8.6.1 Animals and humans exposed to VISUDYNE have been observed to have increased skin photosensitivity reactions. Compounds that quench active oxygen species or scavenge radicals, such as ascorbic acid, bilirubin, and mannitol, would be expected to decrease VISUDYNE activity. Drug interactions decrease recirculation or partial glandular absorption, therefore, their administration could also decrease the efficacy of VISUDYNE in the skin.

8.6.2 Safety and effectiveness in pediatrics patients have not been established.

8.6.4 Pediatric Use
Safety and effectiveness in pediatrics patients have not been established.

5.4 Genotoxicity
An Ames assay performed with VISUDYNE in the presence of metabolic activation by S9 mix was negative. No effects were seen following treatment with S9. A single dose of 100 mg/kg was administered intraperitoneally in B6C3F1 mice to determine the potential for genotoxicity of VISUDYNE. Treatment with VISUDYNE did not cause any increases in the number of aberrant lymphocytes in bone marrow cells and did not cause any increase in micronuclei in rat bone marrow cells, compared to control levels.

5.5 Pregnancy
Due to the potential for photosensitivity reactions upon exposure to light. Use of rubber gloves and eye protection is advised. Patients should be advised to not stay in the dark and should be encouraged to expose their skin to ambient visible light indoors, as it will help inactivate the drug in the skin through a process called photobleaching. Indoor light, as it will help inactivate the drug in the skin through a process called photobleaching.

3.5 PIGMENTS
Indirect ophthalmoscopy, pupillary dilatation, and anterior chamber paracentesis are not possible in patients with dense cataracts. Examination must be done by direct ophthalmoscopy or fundus biomicroscopy.

3.10.2 Diseases that may have a Photosensitive basis
Verteporfin is metabolized to a small extent to its diacid metabolite by liver and plasma esterases. NADPH-dependent deacetylation and NAD-dependent deacetylation are minimal and not pharmacologically significant factors.

2.3 Clinical Pharmacology
The chemical name for the verteporfin regioisomers are:

In a study of patients with retinoblastoma, phototherapy was done with verteporfin for injection and nonthermal red light. In this study, verteporfin therapy was given by intravenous injection under general anesthesia to 31 children aged 1 to 15 years (mean 5.2 years) and 30 adults 16 years of age and older. The study included 4 nonsedated pigs. At a >10-fold higher dose given by bolus injection to sedated or anesthetized pigs, verteporfin caused death within minutes. In cynomolgus monkeys, verteporfin caused an increase in the incidence of anophthalmia/microphthalmia and wavy ribs at doses ≥10 mg/kg/day (approximately 6- to 10-fold the human exposures at the recommended clinical dose).

A2 inhibitors, could also decrease the efficacy of VISUDYNE therapy.

Verteporfin is a 1:1 mixture of two regioisomers (I and II), which are colorless or near colorless liquids, respectively. For the purpose of photodynamically induced tumor destruction, these regioisomers are inefficiently absorbed in vivo. However, under conditions of light sufficient to photoactivate these compounds, the regioisomers are converted to highly reactive, short-lived singlet oxygen and reactive oxygen radicals, which may contribute to observed tumor destruction. For the purpose of phototherapy, visudyne is administered IV in a 1:1 mixture of the regioisomers in a lyophilized form.

Verteporfin is rapidly metabolized by the liver, mainly as unchanged drug. Metabolites are limited and could not be identified by HPLC analysis. They have been characterized by HPLC analysis in extracts from rat, rabbit, and monkey tissue as well as in human postmortem tissue.

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