



Universiteit
Leiden
The Netherlands

Perspectives and update on the global shortage of Verteporfin (Visudyne®)

Sirks, M.J.; Subhi, Y.; Rosenberg, N.; Hollak, C.E.M.; Boon, C.J.F.; Diederer, R.M.H.; ... ; Dijk, E.H.C. van

Citation

Sirks, M. J., Subhi, Y., Rosenberg, N., Hollak, C. E. M., Boon, C. J. F., Diederer, R. M. H., ... Dijk, E. H. C. van. (2024). Perspectives and update on the global shortage of Verteporfin (Visudyne®). *Ophthalmology And Therapy*, 13(7), 1821-1831.
doi:10.1007/s40123-024-00952-9

Version: Publisher's Version
License: [Creative Commons CC BY-NC 4.0 license](#)
Downloaded from: <https://hdl.handle.net/1887/4196104>

Note: To cite this publication please use the final published version (if applicable).



COMMENTARY

Perspectives and Update on the Global Shortage of Verteporfin (Visudyne®)

Marc J. Sirks · Yousif Subhi · Noa Rosenberg · Carla E. M. Hollak · Camiel J. F. Boon ·

Roselie M. H. Diederer · Suzanne Yzer · Jeannette Ossewaarde-van Norel ·

Yvonne de Jong-Hesse · Reinier O. Schlingemann · Rob J. Moss · Elon H. C. van Dijk 

Received: January 9, 2024 / Accepted: April 11, 2024 / Published online: May 16, 2024
© The Author(s) 2024

ABSTRACT

An ongoing global shortage of verteporfin (Visudyne®) limits the treatment possibilities for several chorioretinal diseases, including central serous chorioretinopathy, choroidal hemangioma, and polypoidal choroidal vasculopathy.

Verteporfin is required to perform photodynamic therapy in these ocular diseases. Therefore, the current situation has a substantial impact on eye care worldwide. The worldwide supply of verteporfin appears to be manufactured by a single factory, which is situated in the United States. The distribution of verteporfin is done by different companies for different regions of the world. Official communication

M. J. Sirks · C. J. F. Boon · R. M. H. Diederer
Department of Ophthalmology, Amsterdam
University Medical Centers, University
of Amsterdam, Amsterdam, The Netherlands

Y. Subhi
Department of Ophthalmology, Rigshospitalet,
Glostrup, Denmark

Y. Subhi
Department of Clinical Research, University
of Southern Denmark, Odense, Denmark

Y. Subhi
Department of Ophthalmology, Zealand University
Hospital, Roskilde, Denmark

N. Rosenberg · C. E. M. Hollak
Medicine for Society, Platform at Amsterdam
University Medical Centers, University
of Amsterdam, Amsterdam, The Netherlands

N. Rosenberg · C. E. M. Hollak
Department of Endocrinology and Metabolism,
Amsterdam University Medical Centers, University
of Amsterdam, Amsterdam, The Netherlands

C. E. M. Hollak
Sphinx, Amsterdam Lysosome Center, Amsterdam,
The Netherlands

C. J. F. Boon · Y. de Jong-Hesse · E. H. C. van Dijk (✉)
Department of Ophthalmology, Leiden University
Medical Center, Albinusdreef 2, 2333 ZA Leiden,
The Netherlands
e-mail: ehcvandijk@lumc.nl

S. Yzer
Department of Ophthalmology, Radboud University
Medical Center, Nijmegen, The Netherlands

J. Ossewaarde-van Norel
Department of Ophthalmology, University Medical
Center Utrecht, Utrecht University, Utrecht,
The Netherlands

R. O. Schlingemann
Department of Ophthalmology, Ocular
Angiogenesis Group, Amsterdam University Medical
Centers, University of Amsterdam, Amsterdam,
The Netherlands

R. O. Schlingemann
Department of Ophthalmology, University
of Lausanne, Jules-Gonin Eye Hospital, Fondation
Asile Des Aveugles, Lausanne, Switzerland

R. J. Moss
Dutch National Medication Coordination Centre,
Utrecht, The Netherlands

on the shortage by the responsible companies has been scarce and over the past years several promises with regards to resolution of the shortage have not been fulfilled. The delivery of new batches of verteporfin is at irregular intervals, unpredictable, and may not be fairly balanced between different regions or countries in the world. To ensure a fair distribution of available verteporfin within a country, several measures can be taken. In the Netherlands, a national committee, consisting of ophthalmologists, is in place to arrange this. On the European level, the European Union and European Medicine Agency have plans to monitor medicine shortages more closely and to intervene if necessary. With a more intensified monitoring and regulation of medicine supplies, future impending shortages may be prevented. Remarkably, the amount of medicine shortages is increasing, having a significant and sometimes irreversible impact on patient care. Thus, efforts should be undertaken to minimize the consequences and, whenever possible, to prevent future medicine shortages.

Keywords: Verteporfin; Photodynamic therapy; Central serous chorioretinopathy; Choroidal hemangioma; Polypoidal choroidal vasculopathy

Key Summary Points

An ongoing global shortage of verteporfin (Visudyne®) limits the treatment with photodynamic therapy used for several chorioretinal diseases, leading to possible irreversible vision loss.

The worldwide supply of verteporfin appears to be manufactured by a single factory situated in the United States and is distributed by different companies per region.

Over the past years, deliveries of batches of verteporfin have been scarce, unpredictable, and poorly communicated on by the responsible companies.

National and international steps can be undertaken to monitor medicine shortages, and to fairly distribute remaining medication within the country or within a region.

INTRODUCTION

Since May 2020, there has been a persisting worldwide shortage of verteporfin (brand name Visudyne®) [1]. As verteporfin is required to perform photodynamic therapy (PDT), which is the preferred treatment for several eye diseases, this shortage has a great impact on ophthalmological care worldwide. Despite reported efforts from the manufacturer to restore production of verteporfin, it still cannot be supplied at the required scale, a situation which is expected to last at least until the end of 2024 [1]. This results in patients being undertreated which potentially can lead to irreversible loss of vision [2–4]. This article aims to provide insights into the origin of the shortage, an update on the current standings, suggestions on how we can move forward, and how we could prevent similar issues in the future.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Photodynamic Therapy in Ophthalmology

Verteporfin is used as a photosensitizing agent to perform PDT in several ophthalmological conditions. Verteporfin is injected intravenously over 5–10 min and after injection, it is activated locally in the retina and choroid using illumination with a laser that emits 689 nm wavelength light for a duration of either 42 s (i.e., half-time) or 83 s (i.e., full-time), after which choroidal remodeling occurs [5]. PDT in ophthalmology was first introduced in the year 2000 to treat

E. H. C. van Dijk
Department of Ophthalmology, Alrijne Hospital,
Leiderdorp, The Netherlands

patients with neovascular age-related macular degeneration (nAMD) [6]. Verteporfin is still registered for treating nAMD and for choroidal neovascularization (CNV) that may occur in highly myopic patients. However, in current clinical practice, with the introduction of intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents, the role of PDT in these conditions has been greatly reduced. Still, PDT is deemed to be very effective in several other ophthalmological conditions, mainly those in which a pathological choroidal state is thought to play a pathophysiological role. These include central serous chorioretinopathy (CSC), polypoidal choroidal vasculopathy (PCV), and choroidal hemangioma (CH). For some of these conditions, it is considered the only effective treatment [7–9].

Manufacturing

Verteporfin is currently manufactured in bulk by Alcami Carolinas Corporation (Charleston, SC, USA) for the following distributors: Bausch Health US, LLC (Bridgeport, NJ, USA) for the US market, Neon Healthcare Ltd. (Hertford, UK) for the UK market, and Cheplapharm Arzneimittel GmbH (Greifswald, Germany) for the EU market [10, 11]. It was not possible to identify whether there currently is a sole producer of the active pharmaceutical ingredient (API) or that the API is produced by more companies. However, it seems that there is a single factory situated in the United States, which is responsible for the initial production of verteporfin for the world market. The production of the final product is complex and includes multiple additional ingredients in order to obtain a stable product and part of the process involves freeze drying of the solution.

SHORTAGE

Official Communication on the Shortage

The first mention of the verteporfin shortage by the European Medicine Agency (EMA) was in November 2021 [1]. In this notice it was stated

that there had been a reduction in manufacturing capacity of verteporfin since May 2020, one and a half years before. The cause was said to be a reduction in manufacturing capabilities (defect in the filling machine), after which the manufacturing process was moved to an alternative production line in the same building. In this initial communication, it was said that supplies would be resumed in November 2021 and that the shortage would be resolved by the first quarter of 2022 [12]. It was mentioned that “remaining stocks were distributed in a balanced manner”, and that a small batch of verteporfin was transferred from the United States to the European market [12]. Besides, it was stated that a newly manufactured product had been imported into the EU and was awaiting quality control. Packaging was planned for October 2021 [12].

In a later update in August 2022, it was said that the production of verteporfin was restored in the first quarter of 2022, but at limited capacity [13]. At present, the availability of verteporfin is expected to be limited until the end of 2024 [1]. Again, it was stressed that Cheplapharm will ensure a fair allocation of remaining and newly produced stocks of verteporfin among the affected countries, based on historic demand.

Interestingly, as per March 2023, the website of the American Food and Drug Administration (FDA) marks the verteporfin shortage as “resolved” [14]. The duration of the shortage is listed as running from 18 October 2022 to 9 February 2023. However, insufficient supplies have remained in many parts of the world.

In addition, the website of producer Bausch+Lomb and the English website of Cheplapharm, the market authorization holder for the European market, do not mention the verteporfin shortage.

Hence, contradictory and scattered information by the regulatory authorities, manufacturers, and distributors hampers an accurate topical overview.

Unofficial Communication on the Shortage and Deliveries of Verteporfin Batches in The Netherlands

PDT has been a well-established treatment in the Netherlands for many years. Initially

for nAMD, but in recent years also for CSC and PCV [15–17]. For CSC, this has mainly been based on outcomes of two multicenter randomized controlled trials initiated in the Netherlands, the PLACE and SPECTRA trials, which favored PDT as the preferred first-line treatment [18–22]. Before the shortage, approximately 700 PDT procedures per year were performed in the Netherlands. In these procedures, half the originally described verteporfin dosage (3 mg/square meter of body surface area) was used in most patients with CSC, in accordance with current literature [7]. Over the past few years, the supplies of verteporfin to the Netherlands have been insufficient to treat all patients eligible to PDT. Currently, approximately 50–55% of the normal amount of PDT procedures can be performed. These treatments are allocated to patients selected by a national committee of medical retina specialists, after having discussed each individual patient sent in for review by one of the PDT-performing Dutch centers. Importantly, allocation criteria have been adjusted on a regular basis over these past few years by the national committee. For example, involvement of the Dutch Medication Coordination Centre led to a more future scenario based modeling of supply and demand. However, ad hoc changes in expected deliveries meant that these scenarios had to be adjusted regularly. If the prospects of new supplies were favorable, numbers could be increased to approximately 100 treatments per month, as numerous patients were already waiting to be treated. If expected supplies were more limited, the amount of monthly treated patients had to be reduced to approximately 50 or even 35 cases [2, 3]. This time consuming process has led to delays as well as uncertainty whether the required PDT treatments can actually be executed, which is difficult to accept both for patients and ophthalmologists. Due to the global shortage of verteporfin several countries prohibit export. This hampers the flow of verteporfin amongst countries. National price differences of verteporfin also complicate balancing the available medication by import and export.

Equal Distribution of Verteporfin Batches Between Countries

Despite the official information through EMA from the EU market authorization holder Cheplapharm that mentions assuring a fair allocation of the currently available supplies of verteporfin based on existing demand [13], other information challenges this. Of note, several countries have not received any verteporfin over the last few years [23]. It is thus unclear how this ‘fair allocation’ has been executed.

It appears there are also differences between countries in different regions of the world. This was revealed in the results of the questionnaire that we sent to numerous retinal specialists around the world, which was a part of our previous article [23]. The exact cause for this variation is difficult to establish, and may be multifactorial: different distributors, practice patterns of ophthalmologists, and the possibility of reimbursement for PDT could be of importance.

CURRENT MEASURES

The Netherlands

As we reported in our previous article on the verteporfin shortage, in the Netherlands there is still an active committee of ophthalmologists from all main PDT-treating centers that allocates the available supply of verteporfin to the patients that need it most [23]. This committee was erected in the summer of 2021, shortly after the upcoming shortage of verteporfin was communicated on by Cheplapharm. The committee collectively evaluates all individual cases from within the Netherlands to see if they met their criteria for PDT treatment. The original criteria set by this committee were described in our previous article [23]. These criteria for eligibility for PDT treatment have been adjusted several times based on current and predicted availability of verteporfin. The United Kingdom and France also prioritized specific cases for PDT treatment. In the United Kingdom, available verteporfin was “reserved for the treatment of ocular cancer

patients” [24]. In France, there are still prioritization criteria in effect, and the treating physician can request an ampoule of verteporfin via a form available at the website of Cheplapharm [25]. Denmark had neither a national prioritization strategy nor a committee to evaluate cases for therapy, and treatment was prioritized at each individual center according to obtained verteporfin from time to time at the discretion of the treating physicians [26, 27]. The largest center in Denmark systematically prioritized treatment of CH over cases with CSC. However, the Netherlands had the only committee consisting of representative ophthalmologists from each PDT treatment center, who evaluated every case that might be eligible for PDT treatment. This committee has meetings every month, and currently approximately 50–55% of the usual number of patients can be treated with PDT. With the current outlook on limited supplies of verteporfin, several national authorities have recommended keeping this committee active, and keeping the criteria for allocating treatment with PDT fairly strict. The criteria that are currently used in the Netherlands can be found in Table 1.

European Union

On 25 January 2022, the European Parliament published a new regulation called “REGULATION (EU) 2022/123 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices” [28]. In this regulation, the European Parliament highlights the complexity of shortages of medicinal products and the fact that it is a priority of the European Parliament to further investigate and manage these shortages. For this, the European Parliament announced multiple initiatives, including the erection of the European shortages monitoring platform (ESMP). The ESMP aims to “monitor, prevent and manage actual or potential shortages of medicinal products on the critical medicines lists during public health emergencies and major events” or “actual or potential shortages of medicinal products that are likely to lead to a public health emergency

or a major event” [28]. Additionally, on 11 May 2022, the EMA launched a new committee to oversee medicine shortages and their risks for patient health on a European level [29]. The first meeting of the Executive Steering Group on Shortages and Safety of Medicinal Products (also known as Medicines Shortages Steering Group (MSSG)) has taken place. The MSSG consists of one representative from the European Commission, one representative from the EMA, and representatives from all EU Member States. A larger role for this group is outlined in the proposal for the revision of the pharmaceutical regulation by the European Commission. This includes their participation in establishing a list of critical shortages of medicinal products that require coordination at the EU level [30]. This could possibly facilitate fair allocation of scarce supplies throughout Europe and hopefully address medicine shortages more adequately. Currently, in the case of verteporfin, the MSSG actively monitors the shortage, maintains communication with Cheplapharm, and helps steer toward a solution.

Alternative Treatment Options

With the shortage of verteporfin still current and a limited prospect of a stable supply that is also sufficient to clear the backlog, treating ophthalmologists are being forced not to treat patients who need PDT or to delay treatment. For this very particular situation, alternative options are poor. Due to its complexity and the lack of pharmaceutical-grade active pharmaceutical ingredients, pharmacy compounding was deemed unattainable by hospital pharmacists [31]. As a result, ophthalmologists are seeking alternative medicinal products [15, 32], but no strongly evidence-based alternative treatments with similar efficacy as PDT are currently known. To our knowledge, no other photosensitizers have become available for performing PDT in the eye since our last paper on the verteporfin shortage has been published [23]. Verteporfin dosage reduction is also an option to treat more patients with PDT. Using half-dose PDT had already scientifically been established in the treatment of CSC [7, 8, 15], and to a lesser extent for PCV [33].

Table 1 Prioritization criteria in the allocation of remaining ampoules of verteporfin in the Netherlands, as of January 2024**Category A: Patients with the highest priority of undergoing PDT**

1. Patients with one functional eye or a maximum BCVA of the other eye of 0.5 Snellen decimal with
 - (a) Choroidal hemangioma with submacular fluid
 - (b) CSC with OCT-documented persisting fluid during 3 months with a leakage point that is not accessible for focal laser treatment
2. Children (< 18 years old) with a choroidal hemangioma with submacular fluid
3. Patients with one functional eye or a maximum BCVA of the other eye of 0.3 Snellen decimal with
 - (a) Polypoidal choroidal vasculopathy with foveal intraretinal or subretinal fluid, or (para)foveal hard exudates deteriorating despite 4-weekly intravitreal injections with anti-VEGF agents, after having tried at least two different agents. The polypoidal lesion should not be accessible for focal laser treatment, and should be eligible for treatment with half-dose PDT
 - (b) Non-inflammatory choroidal neovascularization with foveal intraretinal or subretinal fluid, or (para)foveal hard exudates deteriorating despite 4-weekly intravitreal injections with anti-VEGF agents. The patient must have shown insufficient improvement after bevacizumab, ranibizumab, and aflibercept, and one of the following: brolucizumab or faricimab

Category B: Patients with a high priority of undergoing PDT

1. Patients with choroidal hemangioma with extensive subretinal fluid, either macular or extramacular
2. Patients with choroidal hemangioma with submacular fluid and a BCVA of the other eye of > 0.5 Snellen decimal
3. Patients with CSC with OCT-documented persisting subfoveal fluid with a leakage point that is not accessible for focal laser treatment and a BCVA of the other eye of > 0.5 Snellen decimal
For a first episode of CSC, the subfoveal fluid should exist for at least 3–4 months
For a recurrence of CSC within 2 years, the subfoveal fluid should exist for at least 2–3 months
4. Patients with polypoidal choroidal vasculopathy with foveal intraretinal or subretinal fluid, or (para)foveal hard exudates deteriorating despite 4-weekly intravitreal injections with anti-VEGF agents, after having tried at least two different agents. The polypoidal lesion should not be accessible for focal laser treatment, and the BCVA of the other eye may be > 0.5 Snellen decimal

anti-VEGF anti vascular endothelial growth factor, *BCVA* best-corrected visual acuity, *CSC* central serous chorioretinopathy, *OCT* optical coherence tomography, *PDT* photodynamic therapy

For PCV, combination of intravitreal injections with anti-VEGF agents and PDT is recommended in cases where intravitreal injections with anti-VEGF agents alone have had insufficient effect on the presence of intraretinal or subretinal fluid. However, during the verteporfin shortage, ophthalmologists in the Netherlands experienced that patients with PCV may also respond well to monotherapy with aflibercept. This has also been shown in previous literature [34, 35]. If polypoidal lesions in PCV are outside

the macula, patients can also be treated with focal laser [36].

PREVENTIVE MEASURES

Policy and Legislation

With the current abundance in medicine shortages, it is promising that policymakers at the level

of the EU are looking to introduce a more strict surveillance of current shortages to ensure that they are addressed timely. With a more intensified monitoring and regulation of medicine supplies, future impending shortages may even be prevented, for example by upscaling production by other companies through compulsory licensing. In our previous article, we highlighted some possibilities that may help in reducing the consequences of medicine shortages [23]. At a national level, monitoring systems to quickly identify potential shortages have been set up. International collaboration of these initiatives might identify upcoming shortages at an earlier stage. In order to respond to shortages rapidly, a Medication Coordination Centre could be set up to monitor supply and stocks along the supply chain and at end users. If necessary, coordinated redistribution of stocks should be made possible. As of current, market authorization holders are expected to develop shortage prevention and response plans [37]. Besides this, there are other possible measures to prevent medicine shortages. When a market authorization holder expects a reduction in production capability, competitors should be informed of this to allow them to scale up their production, in order to maintain a steady supply to patients within their range of supply. Alternatively, when a patent prevents competitors from producing the same medicine, compulsory licensing can be enforced [38]. This allows other companies to produce the same product despite patent protection, for the purpose of maintaining supplies. Finally, keeping an emergency stock of medication helps prevent temporary shortages. Recently, in July 2022, the Dutch government has reduced this emergency stock requirement from a stock lasting 5 months to 2.5 months [39]. They state that this emergency stock will be able to cover half of temporary medicine shortages. However, it can be discussed whether individual countries should keep emergency stocks or whether this is something that should be managed on a European level.

New Treatment Developments

When there is a lack of a specific medication, replacing this medication with an alternative

compound remains the most straightforward solution. However, for verteporfin, this has been found to be impossible so far. Currently, verteporfin is the only photosensitizer on the market that has the correct safety profile, and pharmacodynamic and pharmacokinetic properties for treatment of the choroid and retina. Past endeavors to develop photosensitizers for eye diseases have unfortunately failed. Some of these have been described in previous publications [23, 40, 41]. Future research could reveal alternative photosensitizers suited for treating chorioretinal diseases.

Sparked by the verteporfin shortage, a study has appeared testing the efficacy of “no-dose” PDT in CSC [42]. In this case, the same laser treatment is used in the eye as with regular PDT, but without the use of any photosensitizer. This small retrospective study without a control group shows that there may be a treatment effect, but further prognostic studies, preferably randomized controlled trials, would have to be performed to provide stronger evidence of its effect for the several diseases in which PDT can be performed.

Finally, a more thorough understanding of pathophysiological mechanisms that play a role in CSC, PCV, and CH may help give new insights leading to the development of new treatment options.

Positive Sides to the Verteporfin Shortage

Although medicine shortages are never welcome, there are some positive sides to the verteporfin shortage that deserve to be mentioned. First, the erection of the national committee allocating verteporfin ampoules has brought some advantages. Given that the Netherlands is a relatively small country (population of roughly 18 million), this committee consisted of ophthalmologists from all centers performing PDT within the country. This allowed a wonderful opportunity for these specialists to meet and discuss cases, and exchange their personal experiences with treatment settings, as well as alternative treatments for several patient categories. For example, for patients with PCV, the previously described aflibercept monotherapy

or focal laser treatment could be considered. In cases with subretinal fluid caused by CSC, the fluid may subside spontaneously without intervention, within 3–4 months. Therefore, it could be advised not to treat these cases with PDT too hastily.

Furthermore, the shortage of verteporfin allowed ophthalmologists to treat their patients with half-dose PDT, instead of full-dose PDT. This has been more established in cases with chronic CSC, but may also have effect in patients with PCV not responding to anti-VEGF monotherapy. The shortage also stimulated ophthalmologists to plan their PDT treatments effectively, such as planning multiple treatments in one day to ensure that all available verteporfin is used as efficiently as possible.

Finally, this period of verteporfin shortage may provide an opportunity for analyzing the results of patients requiring eye care during this time of scarcity. Retrospective analysis of PCV cases may reveal whether patients responded well to alternative treatments such as aflibercept monotherapy or focal laser treatment, or to half-dose PDT. Cases with CSC may be evaluated for the rate of spontaneous resolution of subretinal fluid while awaiting PDT treatment, and the longer term visual acuity after deferred or no treatment.

CONCLUSIONS

The number of medicine shortages is increasing and becoming a topic of debate in both society and politics. The current verteporfin shortage illustrates the complexity and severity of the issue, due to the significant and sometimes irreversible impact on the vision of patients with several different ophthalmological diseases. Thus, efforts should be undertaken to prevent such threatening medicine shortages in the future, particularly when no alternative treatment options exist. However, in the unfortunate event of an unavoidable shortage, international coordination could foster fair allocation and mitigate the impact of the shortage. Although medicine shortages are not preferable, they may also help medical specialists in reconsidering

alternative treatment options and realigning practice patterns with other medical specialists in their field.

Author Contributions. Marc J. Sirks, Yousif Subhi, Noa Rosenberg, Carla E.M. Hollak, Camiel J.F. Boon, Roselie M.H. Diederer, Suzanne Yzer, Jeannette Ossewaarde-van Norel, Yvonne de Jong-Hesse, Reinier O. Schlingemann, Rob J. Moss and Elon H.C. van Dijk contributed to the conceptualization, writing process, manuscript revision, and have read and approved the final manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Yousif Subhi declares to have received speakers fee from Bayer and Roche, not related to this work. Marc J. Sirks, Noa Rosenberg, Carla E.M. Hollak, Camiel J.F. Boon, Roselie M.H. Diederer, Suzanne Yzer, Jeannette Ossewaarde-van Norel, Yvonne de Jong-Hesse, Reinier O. Schlingemann, Rob J. Moss, and Elon H.C. van Dijk declare that they have no competing interests.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the

article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

1. European Medicines Agency. Shortage of Visudyne (verteporfin). 5 November 2021. https://www.ema.europa.eu/en/documents/shortage/shortage-visudyne-verteporfin-supply-shortage_en.pdf. Accessed 19 July 2023.
2. Tsika C, Mohamed MD, Lotery AJ. Impact of the ongoing worldwide shortage of verteporfin (Visudyne®) on the visual function of patients with chronic central serous chorioretinopathy. *Acta Ophthalmol*. 2023. <https://doi.org/10.1111/aos.15714>. Epub ahead of print.
3. Oribio-Quinto C, Fernández-Vigo JI, Bilbao-Malavé V, et al. Anatomical and functional impact of verteporfin shortage in patients with chronic central serous chorioretinopathy. *Photodiagn Photodyn Ther*. 2023;42: 103501.
4. Gawęcki M, Grzybowski A, Pompein-Batkiewicz M. Significant visual impairment after short-lasting central serous chorioretinopathy. *Case Rep Ophthalmol*. 2022;13:678–85.
5. Kwiatkowski S, Knap B, Przystupski D, et al. Photodynamic therapy—mechanisms, photosensitizers and combinations. *Biomed Pharmacother*. 2018;106:1098–107.
6. TAP study group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. *Arch Ophthalmol*. 1999; 117:1329–45.
7. van Dijk EHC, van Rijssen TJ, Subhi Y, Boon CJF. Photodynamic therapy for chorioretinal diseases: a practical approach. *Ophthalmol Ther*. 2020;9:329–42.
8. van Rijssen TJ, van Dijk EHC, Yzer S, et al. Central serous chorioretinopathy: towards an evidence-based treatment guideline. *Prog Retin Eye Res*. 2019;73: 100770.
9. van Dijk EHC, Holtz JK, Sirks MJ, et al. European prevalence of polypoidal choroidal vasculopathy: a systematic review, meta-analysis, and forecasting study. *J Clin Med*. 2022;11:4766.
10. Food and Drug Administration Report. VISUDYNE. Available from: <https://fda.report/DailyMed/952f4c80-50b1-4308-9ee6-311ffeb13df>. Accessed 29 Nov 2023.
11. CHEPLAPHARM Arzneimittel GmbH. VISUDYNE. Available from: https://www.hpra.ie/docs/default-source/Shortages-Docs/visudyne_september-2020.pdf?sfvrsn=2. Accessed 29 Nov 2023.
12. European Medicines Agency. Visudyne (verteporfin): Information on the continuing supply restriction until end Q1/2022. https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-visudyne-verteporfin-information-continuing-supply/2022_en.pdf. Accessed 19 July 2023.
13. European Medicines Agency. Visudyne (verteporfin): Information on the continuing supply limitation until end of 2023. https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-visudyne-verteporfin-information-continuing-supply_en.pdf. Accessed 19 July 2023.
14. United States Food and Drug Administration. Current and Resolved Drug Shortages and Discontinuations Reported to FDA: Verteporfin (Visudyne) Injection. [https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Verteporfin%20\(Visudyne\)%20Injection&st=r](https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Verteporfin%20(Visudyne)%20Injection&st=r). Accessed 19 July 2023.
15. van Dijk EHC, Feenstra HMA, Bjerager J, Grauslund J, Boon CJF, Subhi Y. Comparative efficacy of treatments for chronic central serous chorioretinopathy: a systematic review with network meta-analyses. *Acta Ophthalmol*. 2023;101:140–59.
16. Koh A, Lee WK, Chen LJ, et al. EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina*. 2012;32:1453–64.
17. Lim TH, Lai TYY, Takahashi K, et al. Comparison of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: the EVEREST II Randomized Clinical Trial. *JAMA Ophthalmol*. 2020;138:935–42.

18. van Dijk EHC, Fauser S, Breukink MB, et al. Half-dose photodynamic therapy versus high-density subthreshold micropulse laser treatment in patients with chronic central serous chorioretinopathy: the PLACE Trial. *Ophthalmology*. 2018;125:1547–55.
19. van Rijssen TJ, van Dijk EHC, Tsonaka R, et al. Half-dose photodynamic therapy versus eplerenone in chronic central serous chorioretinopathy (SPECTRA): a randomized controlled trial. *Am J Ophthalmol*. 2022;233:101–10.
20. van Rijssen TJ, van Dijk EHC, Scholz P, et al. Cross-over to photodynamic therapy or micropulse laser after failure of primary treatment of chronic central serous chorioretinopathy: the REPLACE trial. *Am J Ophthalmol*. 2020;216:80–9.
21. Lotery A, Sivaprasad S, O'Connell A, et al. Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2020;395:294–303.
22. Subhi Y, Bjerager J, Boon CJF, van Dijk EHC. Subretinal fluid morphology in chronic central serous chorioretinopathy and its relationship to treatment: a retrospective analysis on PLACE trial data. *Acta Ophthalmol*. 2022;100:89–95.
23. Sirks MJ, van Dijk EHC, Rosenberg N, et al. Clinical impact of the worldwide shortage of verteporfin (Visudyne®) on ophthalmic care. *Acta Ophthalmol*. 2022;100:e1522–32.
24. United Kingdom Department of Health & Social Care, Medicine Supply Notification. Visudyne® (verteporfin) 15mg powder for solution for infusion. Tier 2 – medium impact. Date of issue: 27/5/2021. https://www.rcophth.ac.uk/wp-content/uploads/2021/07/MSN_2021_027-Visudyne-Verteporfin-15mg-powder-for-solution-for-infusion.pdf. Accessed 23 Mar 2024.
25. Rationalisation de l'utilisation des flacons de Visudyne® en février 2023. <https://www.sfo-online.fr/actualites/rationalisation-de-lutilisation-des-flacons-de-visudyne-en-fevrier-2023>. Accessed 23 Mar 2024.
26. Øjenforeningen. Medicin til stressøje kan ikke skaffes. ojenforeningen.dk/artikler/medicin-til-stressoeje-kan-ikke-skaffes. Accessed 23 Mar 2024.
27. Mark J, Subhi Y. Blinded by stress: a patient and physician perspective on central serous chorioretinopathy. *Ophthalmol Ther*. 2024;13:861–6.
28. European Parliament. REGULATION (EU) 2022/123 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2022.020.01.0001.01.ENG&toc=OJ%3A%3A2022%3A020%3ATOC. Accessed 29 Nov 2023.
29. European Medicines Agency. Extended mandate: First meeting of Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG). <https://www.ema.europa.eu/en/news/extended-mandate-first-meeting-executive-steering-group-shortages-safety-medicinal-products-mssg>. Accessed 19 July 2023.
30. European Commission. Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL. https://eur-lex.europa.eu/resource.html?uri=cellar:e3f40e76-e437-11ed-a05c-01aa75ed71a1.0001.02/DOC_1&format=PDF. Accessed 29 Nov 2023.
31. The Dutch Ministry of Health, Welfare and Sport. Kamerbrief over melding medicijntekort Visudyne. <https://www.rijksoverheid.nl/documenten/kamerstukken/2021/07/29/kamerbrief-over-melding-medicijntekort-visudyne>. Accessed 25 July 2023.
32. Larsson JME, Boberg-Ans LC, Vangsted A, et al. Topical non-steroidal anti-inflammatory drugs for central serous chorioretinopathy: a systematic review and meta-analysis. *Acta Ophthalmol*. 2023. <https://doi.org/10.1111/aos.15743>. (Epub ahead of print).
33. Wong IY, Shi X, Gangwani R, et al. One-year results of half- versus standard-dose photodynamic therapy combined with ranibizumab for polypoidal choroidal vasculopathy. *Retina*. 2018;38:725–30.
34. Huang CH, Lai TT, Yang CH, Hsieh YT. Two-year real-world results for aflibercept using the treat-and-extend regimen in neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Ophthalmol Ther*. 2024;13:385–96.
35. Lee WK, Iida T, Ogura Y, et al. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET study: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136:786–93.
36. Sirks MJ, Feenstra HMA, de Vries FR, Dijkman G, Boon CJF, van Dijk EHC. Argon laser photocoagulation in polypoidal choroidal vasculopathy. *Clin Exp Ophthalmol*. 2023;51:177–9.
37. European Medicines Agency. Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf. Accessed 29 Nov 2023.

-
38. 'tHoen EFM, Boulet P, Baker BK. Data exclusivity exceptions and compulsory licensing to promote generic medicines in the European Union: a proposal for greater coherence in European pharmaceutical legislation. *J Pharm Policy Pract.* 2017;10:19.
 39. Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie. Staatssecretaris Blokhuis: ijzeren voorraad geneesmiddelen van tweeënhalve maand. <https://www.knmp.nl/actueel/nieuws/staatssecretaris-blokhuis-ijzeren-voorraad-geneesmiddelen-van-tweeenhalve-maand>. Accessed 29 Nov 2023.
 40. Ciulla TA, Criswell MH, Snyder WJ, Small W 4th. Photodynamic therapy with PhotoPoint photosensitiser MV6401, indium chloride methyl pyropheophorbide, achieves selective closure of rat corneal neovascularisation and rabbit choriocapillaris. *Br J Ophthalmol.* 2005;89:113–9.
 41. Ziemssen F, Heimann H. Evaluation of verteporfin pharmacokinetics—redefining the need of photosensitizers in ophthalmology. *Expert Opin Drug Metab Toxicol.* 2012;8:1023–41.
 42. Servillo A, Sacconi R, Zucchiatti I, et al. No-dose photodynamic therapy against half-dose photodynamic therapy for treatment of central serous chorioretinopathy. *Ophthalmol Ther.* 2023;12:2199–208.
-