

BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)

June 2017
Review: June 2020

Bulletin 254: Photodynamic therapy (PDT) with verteporfin (Visudyne®) for chronic central serous retinopathy

JPC Recommendations:

- To support the use of PDT with verteporfin for the treatment of **Chronic** Central Serous Retinopathy.
- Approval is subject to patient outcomes being provided (via Blueteq reauthorisation process).

New Medicine Review – Bulletin

Medicine	Photodynamic therapy (PDT) with verteporfin (Visudyne®) for chronic central serous retinopathy
Document status	Second version (update of review completed in 2012) – Final approved post June 2017 JPC meeting.
Date of last revision	June 2017
Proposed Sector of prescribing	Secondary care
Introduction	<p>Central serous chorioretinopathy (CSC) is a rare condition characterised by the accumulation of subretinal fluid between the neurosensory retina and the retinal pigment epithelium (RPE) (1). It is commonly associated with fluid accumulation under the macula and detachment of the retina. When the detachment occurs in the central macula, symptoms may include reduction of best-corrected visual acuity (BCVA). (1-3)</p> <p>Although most cases are acute (with spontaneous resolution and minimal sequelae), some patients have a more chronic version of the disease with poorer visual prognosis. People with chronic CSC with long-standing subretinal fluid accumulation may develop RPE atrophy and changes in the neurosensory retina that result in a permanent loss of visual function. (1-3)</p> <p>One-third to one-half of CSC cases will recur in one year. A waxing and waning course is not unusual and contributes to the difficulty in attributing visual improvement to treatment benefit. (3)</p>
Summary/ Key points	<p>PDT with verteporfin is a newer treatment modality for CSC, first reported in 2003. At present, it is typically used in cases of CSC involving the macula that have not responded to other treatments or observation (3).</p> <p>There are no national guidelines on the management of this rare condition and currently no evidence-based consensus on its management. A recent Cochrane network meta-analysis concluded that overall the current evidence for any intervention for the treatment for CSC is low to very low; however that for PDT is ‘somewhat stronger’.</p> <p>The majority of the published data available for verteporfin PDT in chronic CSC are uncontrolled prospective or retrospective studies; only limited and very small randomised controlled trials are available. The protocols evaluated (dose of verteporfin and fluence) have varied; the majority of more recent studies have utilised half (or lower) dose verteporfin. The primary outcomes evaluated have varied between studies but overall the available data suggest that PDT is associated with stable or improved vision in the majority of patients with chronic CSC, often with complete resolution of subretinal fluid. Recurrence has occurred but usually responds to retreatment.</p> <p>The use of lower fluence PDT and lower doses of PDT have been suggested as a way of reducing adverse effects. One small RCT has compared different PDT doses and reported similar visual acuity improvements for full-dose and 50% PDT; recurrence rate appeared to be higher in the lower dose group but the difference between groups was not statistically significant. Other lower quality data are available suggesting similar outcomes for full versus half-dose PDT and full versus half-fluence PDT but the lack of randomised data means it is not possible to make any conclusions as to their relative efficacy and long-term safety. The optimal schedule (dose and fluence) remains to be determined.</p>

<p>The intervention</p> <p>Mechanism of action</p>	<p>Verteporfin (Visudyne®, Novartis) is a light-activated drug which must be used in combination with laser therapy of a specific wavelength. This is known as photodynamic therapy (PDT).</p> <p>Verteporfin is a mixture of benzoporphyrin derivative monoacids that are only cytotoxic when activated by light in the presence of oxygen. It is administered by IV infusion and is activated by light waves of a specific frequency that are applied into the eye(s). Once activated, verteporfin exerts its action through oxidative reduction of tissues leading to tissue destruction and cell death.</p> <p>The mechanism of action of verteporfin PDT in CSC is postulated to be a reduction in choroidal congestion, vascular hyperpermeability and extravascular leakage (8). Generally, PDT causes the complete resolution of subretinal fluid in CSC; recurrences do occur but they appear to be responsive to re-treatment.</p> <p>The selectivity of PDT using verteporfin is based, in addition to the localised light exposure, on selective and rapid uptake and retention of verteporfin by rapidly proliferating cells including the endothelium of choroidal neovasculation. (4-6)</p>
<p>Licensed indications</p>	<p>Verteporfin is licensed in the UK for the treatment of (6):</p> <ul style="list-style-type: none"> - adults with exudative (wet) age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularisation (CNV) - adults with subfoveal CNV secondary to pathological myopia <p>It has also been investigated for several other ophthalmological indications.</p>
<p>Usual dosage</p>	<p>For its licensed indications, verteporfin is used at a dose of 6mg/m² body surface area (BSA), diluted in 30mls of infusion solution and administered by IV infusion over 10 minutes. Light activation is then performed 15 minutes after the start of infusion. This involves use of a diode laser generating non-thermal red light (wavelength 689 nm ± 3 nm) via a slit lamp mounted fibre optic device and a suitable contact lens. At the recommended light intensity of 600mW/cm², it takes 83 seconds to deliver the required light dose of 50 J/cm². (6)</p> <p>PDT for the treatment of CSC first employed the standard dose of verteporfin (as recommended for its licensed indications); however more recent reports describe the use of amended parameters, such as a reduced dose of verteporfin or reduced irradiation, in order to reduce potential side-effects (7).</p>
<p>Treatment alternatives/ place in therapy</p>	<p>There have been a variety of interventions used, or proposed for use, in CSC, including laser treatments, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents; medications that alter steroid hormones; and others (4). There is however at present no evidence-based consensus on its management. Laser photocoagulation can only be used where the treatment area is well defined and cannot be used in the centre of the fovea due to concerns of incidental damage (5).</p>
<p>Future alternatives</p>	<p>None apparent</p>
<p>National guidance</p>	<p>None available</p>
<p>Evidence for use</p>	<p>Several groups have investigated the use of PDT with verteporfin for chronic forms of CSC and selected cases of acute CSC. Generally, PDT causes the complete resolution of subretinal fluid in CSC; recurrences do occur but they appear to be responsive to re-treatment (4).</p> <p>There is an abundance of published data regarding this intervention but in general a lack of randomised controlled trials which makes it difficult to draw firm conclusions. In addition the available studies have utilised different doses of verteporfin and different fluences, and due to the lack of a gold standard treatment for CSC, there has been no standard comparator. Where comparative data are available, the comparator used has often been PDT itself, with amended parameters, or another intervention (such as anti-VEGF) for which the data are also of limited quality. The studies are also complicated</p>

by the fact that the disease may have a waxing and waning course, which contributes to the difficulty in attributing visual improvement to treatment benefit (3). The rarity of CSC would make it difficult to recruit enough patients for a high quality randomised controlled trial.

With this in mind, the available published data are discussed below and further in Table 1 (see Appendix). Please note that there is an abundance of data of a similar quality and therefore only the more robust studies (prospective, randomised) and the largest non-randomised data sets have been included.

Please note: Data for the use of one-third dose verteporfin and very minimal fluence PDT are now appearing in the literature but are very limited and have been referred to only briefly here.

Statistical vs Clinical Significance – the following information will assist in the assessment of statistical vs clinical significance of the outcomes shown in the clinical trial evidence presented.

One ETDRS line (five letters) is equivalent to 0.1 logMAR; thus, logMAR values can be converted to ETDRS letters correctly seen for ease of interpretation, using the following equation:

$$100 - (50 * \log\text{MAR})$$

The degree of improvement in logMAR or ETDRS letters that is considered clinically important is uncertain and has varied among studies. Statistically significant changes in visual acuity may not necessarily be clinically relevant. The minimal clinically important difference reported in the literature is five to 10 ETDRS letters (one to two lines).

<https://www.ncbi.nlm.nih.gov/books/NBK169468/#!po=12.5000>

Full-dose (standard) verteporfin and full-fluence PDT

There have been no randomised controlled trials comparing full-dose verteporfin, full-fluence PDT with sham/no treatment.

Numerous case series evaluating standard-dose verteporfin (6mg/m² body surface area) have however been published. The largest included 82 consecutive cases of chronic CSR in 72 patients (mean age 46 years range 29 to 70 years), with a mean length of follow up of 12 months (range 3-48 months) (9). Various inclusion criteria were applied, including persistent CSC of >6 months duration (average duration was 28 months; range 6-240 months) or RPE changes induced by multifocal recurrent detachment. The results found:

- BCVA improved in 67% of cases. Mean logMAR BCVA changed from 0.53 (standard deviation [SD] 0.43) before PDT to 0.38 (SD 0.41) at 3 months and 0.48 (SD 0.5) at 6 months (p<0.0001 and p=0.007 respectively).
- Mean BCVA at the end of follow up was 0.37 (SD 0.45, p< 0.0001 from baseline).
- Macular detachment resolved and subretinal fluid disappeared in all cases.
- Central foveal thickness decreased from 325 micrometres (SD 95) to 229 micrometres (SD 70) at 1 month after PDT, 206 micrometres (SD 68) at 3 months and 202 micrometres (SD 76) at 6 months (p<0.0001 for all).
- Reactive RPE hyperplasia was observed in 9 cases following PDT

Overall, 69 eyes required only one PDT session to achieve complete resolution of subretinal fluid and 13 eyes required more than one session (range 2-4 sessions). The researchers conclude that PDT with verteporfin may be useful in the treatment of patients with chronic CSC, with a rapid resolution of subretinal fluid followed by improvement and/or preservation of vision. They add, though, that the safety and

efficacy of this approach needs to be explored further with larger randomised studies with longer follow up.

Other published non-comparative case series (prospective and retrospective) are summarised in Table 1 (10-14). Where reported, complete resolution of subretinal fluid was seen in almost all patients treated. The reporting of visual outcomes differed between studies – some reported the percentage who had a gain in at least two (30%) or three (27%-69%) lines from baseline, or the average number of ETDRS lines gained (0.55 lines 6 weeks; 2 lines at 12 months; 8 letters at 48 months); others reported change in BCVA (logMAR) (mean improvement of 0.16-0.18). One small retrospective case series (n=29) reported that visual outcomes with intravitreal bevacizumab were similar in terms of gains in mean visual acuity over the short-term (mean follow-up 5-7 months); visual recovery was however slower with the latter and fluctuating and 25% developed disease recurrence (mean 3.5 doses administered) (15).

Full-fluence versus reduced-fluence

It has been suggested that the irradiation used in standard-fluence PDT may exceed that necessary to activate verteporfin, and could activate the photosensitiser also in the choriocapillaris surrounding the irradiated area, resulting in unwanted or undesirable damage to normal tissue. Choroidal damage may be affected by the fluence rate and thus may be avoided by use of an appropriate fluence (8).

No randomised controlled trials comparing full-fluence and reduced-fluence PDT, or reduced-fluence and sham/no treatment were located.

A prospective, non-randomised clinical trial has compared the efficacy and safety of half-fluence (25 J/cm²) versus full-fluence (50 J/cm²) verteporfin PDT for CSC (8). It included 42 patients (42 eyes) with a BCVA of 0.2 to 1.0 logMAR who had subretinal fluid in the foveal region for ≥3 months and who had not been previously treated with focal laser therapy or PDT. At 12 months the visual acuity improved from a mean of 0.46 to 0.16 logMAR in the low fluence group and from 0.43 to 0.24 logMAR in the standard group (both p<0.05 vs. baseline; no difference between groups). Complete subretinal fluid reabsorption was seen in 15 standard-fluence and 21 low-fluence-treated eyes (79% vs. 91%; p=0.5) (8).

Two further retrospective case series have compared outcomes of patients receiving full or half-fluence PDT for chronic CSC (>3 months). The first (68 eyes) reported a decrease in subfoveal choroidal thickness (SFCT) in both groups; the reduction was however greater in the full-fluence group (decrease from 351±70 µm at baseline to 267±66 µm at 12 months; 362 ± 63 µm and 318 ±76 µm, respectively, in the half-fluence group; p=0.001). Both BCVA and CRT improved after PDT in both groups (p<0.001); the differences between the groups were not significant. With a mean follow-up of approximately 15 months, two cases of recurrence were observed in the half-fluence group, whereas no recurrence was seen in the full-fluence group (16). The second (67 eyes) reported similar improvements in both groups (17). There was complete resolution of subretinal fluid in 94.1% of those treated with half-fluence and 100% of those treated with full-fluence PDT (difference p=NS). Visual acuity was improved in both groups (from 0.34 ± 0.27 at baseline to 0.17±0.32 at last follow-up in the low-fluence group vs. 0.46 ± 0.42 to 0.21±0.39, respectively, in the conventional group; p=0.603). Both of these studies used a new method to measure choroidal hypoperfusion following PDT, and, using this, suggest that half-fluence PDT had a smaller negative effect than conventional PDT.

A further retrospective study compared full fluence and half-fluence when used in conjunction with half-dose verteporfin (18). This reported better outcomes associated with standard fluence PDT versus half-fluence PDT, when used in conjunction with half-dose verteporfin; for example complete resolution of subretinal fluid was seen more frequently (93% versus 64%; p=0.031) and mean BCVA improvements were higher (0.626 ± 0.398 at baseline to 0.292 ± 0.486 at 6 months versus 0.799 ± 0.572 to 0.669 ± 0.569).

Further, randomised studies of a longer duration are required to confirm the initial findings that suggest low-fluence PDT is associated with less choroidal hypoperfusion than standard-fluence PDT, and determine what the clinical outcomes of such differences. Although the described studies suggest that improvements in visual acuity with the low-fluence PDT appear to be broadly similar to those seen with the standard-fluence PDT, further studies of a better quality are needed. Further studies combining low-dose verteporfin and reduced fluence PDT are also required as the pilot study discussed above, although of a low quality, suggests a lower success rate with this protocol.

Half fluence versus half-dose PDT

A randomised, prospective observer-masked study compared the efficacy and safety of half-dose verteporfin (3mg/m²; standard fluence) and half-fluence PDT (42 seconds of laser light - 25J/cm²; with full-dose verteporfin) for CSC (19). It included 40 patients (40 eyes) with symptomatic CSC of 4-month duration of more and active leakage in the fluorescein angiography with mean age 45-46 years old. Primary outcome measures were the changes in BCVA and in central retinal thickness (CRT) and subretinal fluid in OCT. Follow-up was for 6 months and the findings were as follows:

- The BCVA (logMAR) in the half-dose group was 0.39±0.28 (Snellen equivalent =6/15) at baseline, which improved to 0.33±0.31 at 1 week, 0.22±0.33 at 1 month, 0.16±0.29 at 3 months, and 0.15±0.31 at 6 months (comparisons all statistically significant versus baseline).
- The BCVA (logMAR) in the half-fluence group was 0.36±0.41 (SE6/13.7) at baseline, 0.26±0.34 at 1 week, 0.17±0.36 at 1 month, 0.13±0.33 at 3 months, and 0.12±0.33 at 6 months (comparisons all statistically significant versus baseline).
- CRT was also significantly improved at all post-PDT time points in both fluence groups (p<0.05).
- All patients in the half-dose group and 19 patients (95%) in the half-fluence group had complete absorption of subretinal fluid at post-PDT 3 and 6 months.
- The degree of choroidal hypoperfusion seen after treatment was similar for both groups.

There were no statistically significant differences in any measurement between the two groups. The authors concluded that both half-dose and half-fluence modifications of PDT were similarly effective in improving the visual acuity and subretinal fluid for chronic CSC. No systemic or ocular complications were seen in any of the patient in both groups throughout the study period.

Low-fluence PDT and half-dose PDT have also been compared in several retrospective studies; the largest are summarised in Table 1 (20-24). The results of these also suggest similar outcomes between the two regimens; although some small differences (not statistically significant) were noted in some studies.

Half fluence versus other comparators/ no comparator

Two small randomised pilot studies have compared low-fluence PDT to intravitreal ranibizumab (16 eyes) or bevacizumab (n=22) (2, 25). The Cochrane review pooled the results of these two studies and noted that mean change in visual acuity was similar between PDT and anti-VEGF groups (although the mean result of 0.03 logMAR was in favour of PDT, the confidence intervals crossed 1 [-0.08 to 0.15]). There was a higher risk of recurrence in the anti-VEGF groups but the magnitude differed widely between the studies. The quality of evidence was noted to be low/very low due to risk of bias and imprecision (4).

A further four case series (n ranging 20-38 eyes) describing patients treated with half-fluence PDT are summarised in Table 1 (26-29). With follow-up ranging up to 44 months, the results show improvements in visual acuity, with resolution of subretinal

fluid in 87-100% of eyes treated. The study with the longest follow-up reported that one patient (out of 34) required retreatment; one patient went on to develop CNV four years later and received anti-VEGF injections. Please see Table 1 for further details.

Half-dose PDT

A randomised study comparing half-dose verteporfin and half-fluence PDT has already been discussed above (19).

The Cochrane review identified one randomised controlled trial (n=60) that compared full-dose PDT to 50% PDT and 30% PDT, and summarises the following key results with respect to half versus full-dose (the article itself was published in a Chinese journal so has not been referred to directly) (4; 46):

- The mean change in visual acuity was 0.23 logMAR (SD 0.15) for the 50% PDT group and 0.19 logMAR (SD 0.16) for the full-dose PDT group (the 95% CI for the mean difference however crossed 1 [MD 0.04, 95% CI -0.04 to 0.12] and this was considered to be low quality due to this imprecision and the risk of bias).
- CSC resolved in all 30 eyes in the 50% PDT group; 10 of these had a recurrence by 12 months. Resolution was also seen in all 30 eyes in the full-dose PDT group, with recurrence in 8 (RR 1.25, 95% CI 0.57 to 2.73). This was again judged to be low quality as the CI crossed 1 and there was risk of bias.

A retrospective review including 192 patients (192 eyes; mean age 45 years) compared outcomes of patients with CSC treated with half-dose verteporfin PDT (n=75) and those who were untreated (controls; n=117) (30). All patients were offered the treatment option of using half-dose verteporfin PDT for CSC if the subretinal fluid persisted for more than 3 months or if the patients requested early treatment due to progressive visual loss. The minimum follow up of all patients was 36 months (mean 74.1 months). The main findings are as follows:

- At the last follow-up, the mean logMAR was significantly better in the half-dose verteporfin PDT group vs. untreated control group (p=0.005)
- The mean visual improvement of the half-dose verteporfin PDT group at the last follow-up was 1.8 lines, compared with 0.0 lines in the untreated group (p<0.001)
- Recurrence of CSC developed in 15 eyes (20%) in the half-dose verteporfin PDT group vs. 63 eyes (53.8%) in the untreated group (p<0.001)
- Survival analysis demonstrated that eyes treated with half-dose verteporfin PDT were significantly less likely to develop CSC recurrence compared with untreated controls (p<0.001) and regression analysis showed that half-dose verteporfin PDT was the only significant factor in reducing the risk of CSC recurrence.

A small prospective case series (n=26) compared half-dose verteporfin PDT to focal laser photocoagulation (FLP) and reported mean visual acuity improvements in both groups, that were larger in the FLP group (mean logMAR 0.22±0.18 at baseline to 0.04±0.07 after 1 month [p=0.044] and 0.14±0.16 to 0.07±0.13 with PDT [p=0.059]). Complete absorption of retinal fluid was however seen more frequently in the PDT group (13/14 versus 7/12 FLP) (34).

A prospective, non-randomised study compared half-dose verteporfin PDT (n=24) and subthreshold diode-laser micropulse (SDM; n=20) to a control group of patients who received observation only (n=18) (45). At 16 weeks BCVA had improved by 8.5 ETDRS letters in the half-dose verteporfin group, by 6.7 letters in the SDM group, and by 1.5 letters in the control group. Both active treatments were also associated with significant improvement in reduction of leakage activity compared to the control group.

A handful of small prospective, non-comparative case series have evaluated half-dose verteporfin PDT (31-33). The largest (n=48), with a follow-up of 12 months, reported mean visual acuity improvements (from 0.31 LogMAR at baseline to 0.15 LogMAR at

	<p>12 months [$p < 0.001$]; mean of 1.6 [range -5 to 8] ETDRS lines gained after 12 months). The mean number of treatments was 1.2 per eye, with 11/48 requiring a repeat treatment (six had resolution and five persistent problems) (31). Other, smaller studies with varying follow-up report similar findings; one with a mean follow-up of two years ($n = 27$ eyes) reported complete resolution of subretinal fluid in all eyes initially, with two recurrences. Mean visual acuity was improved at all time points versus baseline (0.19 ± 0.27 logMAR at baseline, 0.10 ± 0.20 at 1 month, 0.09 ± 0.20 at 3 months, 0.08 ± 0.20 at 6 months, 0.07 ± 0.20 at 12 months, and 0.09 ± 0.25 at 24 months) (32).</p> <p>Outcomes with half-dose verteporfin PDT have also been evaluated in a number of retrospective, non-comparative case series; the largest of which are summarised in Table 1 (35-39).</p> <p>Acute CSC</p> <p>There has been a randomised placebo-controlled trial of half-dose verteporfin PDT for the treatment of <i>acute</i> CSC, which included 63 patients (63 eyes) with symptomatic idiopathic CSC of 3 months' duration or less (40). The primary outcome measure was the proportion of eyes with absence of subretinal fluid at the macula at 12 months – this occurred in 37 (94.9%) eyes in the verteporfin group compared with 11 (57.9%) eyes in the placebo group ($p = 0.001$). The Cochrane review included this as the only randomised controlled comparison of PDT versus no PDT in CSC. Although PDT was associated with visual acuity improvements (mean difference of -0.10 logMAR 95% CI -0.18 to -0.02) and a lower rate of recurrence, this was considered low evidence due to risk of bias and imprecision (as either the confidence intervals included one or there were very few events).</p> <p>Other regimens</p> <p>The Cochrane review identified two randomised studies comparing 30% and 50% PDT (one also including a full-dose PDT comparison arm; already discussed above in the half-dose section) (41, 42). The mean change in visual acuity favoured the 30% PDT group over both 50% (mean difference of -0.12 logMAR, 95% CI -0.15 to -0.08) and full-dose PDT (MD -0.16, 95% CI -0.22 to -0.10). The risk of recurrence was however higher with 30% compared to 50% (RR 2.50, 95% CI 1.54 to 4.06; moderate quality evidence) and full-dose PDT (RR 2.75, 95% CI 1.46 to 5.17). CSC persistence at 12 months was also higher in the 30% group compared with the 50% group.</p> <p>A small pilot study has compared half-dose PDT to pseudo-PDT (689 nm laser treatment delivering 95 J/cm^2) in 20 patients with chronic CSC (43). This found the visual acuity improvements between the two groups to be comparable (gain of 7.3 +/- 1.3 ETRDS letters in the half-dose PDT group and 7.6 +/- 1.5 ETRDS letters in the pseudo-PDT group after 16 weeks; $P = 0.64$).</p>
Safety	<p>The most frequently reported adverse reactions to verteporfin are injection site reactions (including pain, oedema, inflammation, extravasation, rashes, haemorrhage, discolouration) and visual impairment (including blurred, fuzzy vision, photopsia, reduced visual acuity and visual field defects, including scotoma and black spots). Most adverse reactions to verteporfin seen in the clinical studies upon which licensing was based were mild to moderate and transient in nature (6).</p> <p>In terms of CSC specifically, there may be dose-dependent complications such as the development of RPE atrophy, choriocapillaris ischemia, CNV, and RPE tear (4).</p> <p>A larger retrospective study with a mean follow-up of 36 months reported treatment complications in 8 eyes (5.9%), including enlarged RPE atrophy (5 eyes), CNV (1 eye), RPE rip (1 eye) and subretinal fibrotic macular scar (1 eye) (37).</p>
Costs Tariff status Activity costs	<p>Drug costs only – £850 for a 15mg vial of verteporfin (assuming this is one dose, with single patient use) (44)</p> <p>Other costs will need to be taken into account – including those associated with day-</p>

	case admission, administration, imaging, follow-up assessments, etc.	
Costs of alternatives	Ranibizumab	Ranibizumab (Lucentis®) 10mg/mL, net price 0.23mL vial = £551 (44)
	Bevacizumab	Unlicensed intravitreal bevacizumab costs around £150 per dose
	[Please note that the above are drug costs only and the cost of any non-drug alternatives have not been considered. Please also note that bevacizumab is not licensed for intravitreal use and neither bevacizumab nor ranibizumab are licensed for the treatment of CSC].	
Cost effectiveness (if available)	No cost-effectiveness data were identified.	
Potential number of patients in Bedfordshire and Luton Impact per 100,000 population	Prevalence of 5.8 per 100,000 population although the majority of these will resolve spontaneously and others will be acute (5). Local information:- LCCG has received 2 requests for verteporfin/PDT for the treatment of Chronic Central Serous Retinopathy in the last 2 years while BCCG has received no requests. (The last time that BCCG received a request was in 2012 when 5 requests were received).	
Affordability considerations		
Patient choice/ access Considerations Decisions from other bodies/	No national guidance or decisions on use of verteporfin PDT for CSC.	
Points for consideration	There is currently no gold standard treatment for chronic CSC. The evidence for any treatment for this rare condition is limited.	
Limitations of review	There is a lack of randomised studies evaluating PDT with verteporfin for CSC; most data are case series with the associated potential biases. The majority of studies lack an observational control group, so it is not possible to compare outcomes of treatments with the natural course of the disease. Although the general quality of the available evidence for verteporfin PDT is limited, there is an abundance of lower quality data suggesting that it is associated with mean improvements in visual acuity (varied measures and various results reported) and complete resolution of subretinal fluid in the majority of patients treated. Although in the reported studies the majority of patients had only one treatment (although follow-up has been limited), treatment may need to be repeated in some patients. Further, longer-term data is required to determine recurrence rate and longer-term safety. The optimal treatment schedule (in terms of fluence and verteporfin dose) remains to be confirmed.	

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

APPENDIX: Table 1: Studies of verteporfin PDT in CNV secondary to CSC (>15 eyes)

Author	Design	Population	Treatment	Follow-up (months)	Efficacy outcomes
Standard dose PDT					
Ergun (11)	Prospective, non-comparative case series	Subfoveal CNV secondary to CSC 24 pts (26 eyes) Mean age 57 (range 36-78)	PDT Mean of 2.6 treatments per patient	6-36 (mean 22) months	<ul style="list-style-type: none"> At 6 months 27% had gain in VA \geq 3 lines; 62% remained stable (within 2 lines) and 12% lost \geq3 lines Relative results for one year (2 lost to follow-up) were 50%, 38% and 13% Mean gain of one line at 6 months and 2 lines at 12 months Mean gain of 0.09 logMAR units (p=NS) at 6 mo and 0.16 at 1yr (p=0.03 vs. baseline)
Piccolino (12)	Non-comparative case series*	CSC and macular detachment unresponsive to previous FLP 16 pts Mean age 59 (range 49-79)	PDT	6-12 months	<ul style="list-style-type: none"> Serous detachment resolved in 12 eyes (75%) Retinal thickness decreased in 2 eyes with cystoid macular changes Macular exudation resolved completely in 13 eyes (81%) Two eyes were unchanged and a further PDT resulted in partial regression After 3 mo, VA improved from 1 to 4 lines in 11 (69%) and was unchanged in 5 (31%)
Yannuzzi (13)	Prospective non-comparative case series*	Chronic CSC 15 pts (20 eyes)		Mean 6.8 months (range 4-12.5)	<ul style="list-style-type: none"> Visual acuity improved by \geq2 lines in 6 eyes (30%) and remained stable in 14 (70%) All cases had complete resolution ICG hyperpermeability at the site of treatment 2-6 wks after treatment Mean visual acuity improved by 0.55 lines after six weeks (considered marginally significant) Visual improvement was only observed in those whose VA was 20/100 or better prior to treatment
Vasconcelos H et al (10)	Retrospective case series	15 pts (17 eyes) Mean age 48 years	Standard PDT	80.6 \pm 12.4months (62-104 months)	<ul style="list-style-type: none"> All eyes had neurosensory detachment at baseline, at final visit all eyes had resolution of neurosensory detachment, with a statistically significant reduction in central macular thickness ([=0.05], and a preserved neuroretinal thickness 9p=0.839). Mean BCVA increased from baseline with a gain of 8.4\pm7.8 letters (p<0.001) at final follow-up.
Silva (14)	Retrospective case series	Chronic CSC 42 pts (46 eyes) Age range 30-72 years	All PDT Mean 1.08 treatments	Minimum 48 months	<ul style="list-style-type: none"> Mean BCVA improved from 58.8 letters at baseline to 66.9 letters at month 48 (p<0.01) Complete resolution of SRF in 93.4% No side effects reported
Lee (15)	Retrospective case series	29 pts (29 eyes) Detachment of retina >6 mo (or recurrent) No evidence of CNV Mean age 48 No previous treatment with LP	Beva (n=16) vs PDT (n=13)	Beva - 7.3 months PDT -5.9 months	<ul style="list-style-type: none"> Mean BCVA (logMAR) improved from 0.32 \pm 0.28 to 0.18 \pm 0.26 (p=0.06) in the beva group (mean 3.5 doses) and from 0.37 \pm 0.15 to 0.19 \pm 0.18 in the PDT group (single treatment) Mean FT fell from 290 to 219 μm, and from 332 to 171 μm, respectively Complete resorption of SRF was seen in 12pts (92%) in the PDT group Visual recovery in the beva group was slower and fluctuating; 4 eyes developed disease recurrence and 3 developed drug resistance following repeated injections

Author	Design	Population	Treatment	Follow-up (months)	Efficacy outcomes
Half-dose verteporfin versus half-fluence PDT					
Alkin et al (24)	Retrospective comparative Review	60 pts (64 eyes)	Low fluence PDT (36 eyes) Half-dose PDT (28 eyes)	12.5±4.3 in low-fluence group and 13.1±4 months in half-dose group	<ul style="list-style-type: none"> 33 eyes (91.6%) in the low-fluence group and 26 eyes (92.8%) in the half-dose group showed complete resolution of SRF (p=0.703) Mean BCVA increased by 7.4 letters and 4.8 letters in the low-fluence group and the half-dose group, respectively (p=0.336) Seventeen eyes (52.8%) in the low-fluence group and 14 eyes (50%) in the half-dose group experienced a gain of at least 5 letters in BCVA (p=0.825) Significant decreases in the central foveal thickness were seen in both groups
Nicolo M et al (20)	Retrospective comparative case series	56 patients (61 eyes)	Half-fluence PDT (31 eyes) Half-dose PDT (29 eyes)	12	<ul style="list-style-type: none"> Mean logMAR BCVA improved significantly at 12 months in both the half-fluence group (from 0.187 ± 0.187 to 0.083 ± 0.164) and the half-dose group (from 0.126 ± 0.091 to 0.68 ± 0.091) without significant difference between the two groups. At 12 months a complete resolution of SRF was achieved in 26 half-fluence-treated eyes (83.9%) and 29 half-dose treated eyes (100%) (p=0.529). Nine eyes (29%) in the half-fluence group and 5 eyes (17.2%) in the half-dose group had at least one recurrence of SRF during follow-up (overall 15 and 5 recurrences, respectively (p=0.07) Atrophy of the retinal pigment epithelium was not observed in either group.
Kim YK et al (21)	Retrospective comparative case series	52 patients (52 eyes) Mean 46 years	Half-dose PDT (n=26) Half-fluence PDT (n=26)	Half-fluence group 20.7±7.2 and for half-dose group 22.3 ± 6.1	<ul style="list-style-type: none"> In half-fluence PDT group, mean BCVA improved significantly (p<0.001) from 0.31 ± 0.29 at baseline to 0.11 ± 0.20 at final follow up (≥ 12 months), and for half-dose group, mean BCVA improved significantly (p<0.001) from 0.31 ± 0.20 to 0.12 ± 0.20 at final follow up (≥ 12 months). There was no significant difference between the groups. No significant difference in any measures between the groups.
Shiode Y et al. (22)	Retrospective comparative case series	43 patients (45 eyes) SRF due to CSC for at least 3 months No prior treatment Mean age 60-63 years	Half-dose PDT (n=37) Half-time PDT (n=18)	3	<ul style="list-style-type: none"> One month after treatment, SRF completely resolved in 8 eyes given half-time dose and 14 eyes given half-doses (44.4% vs. 51.9%, p>0.1). After 3 months serous retinal detachment resolved in 88.8% of patients in both groups (p=NS) In half-time group, BCVA improved from baseline of 0.245 to 0.130 at 3 months, and in half-dose group from 0.283 to 0.138 – both were significantly improved from baseline at 3 months (p<0.01), with no difference between groups. Significant reductions in CRT were seen in both treatment groups at 3 months vs. baseline (p<0.05), and the difference between the groups was not significantly different) No systemic/ocular adverse effects developed over follow-up period
Liu H et al (23)	Retrospective comparative case series	61 eyes with acute or chronic CSC including fovea	Half dose PDT (n=35) Half time PDT (n=26)	14.8 ± 13.3	<ul style="list-style-type: none"> Significant improvement in BCVA at each follow-up for both groups (p<0.001 for all). For example half-dose PDT group changed from baseline of 0.39 ± 0.2 logMAR at baseline to 0.25 ± 0.19 logMAR at 12 months (p<0.0002 for all). For half-time PDT - 0.29 + 0.20 logMAR at baseline to 0.15 ± 0.09 logMAR at 12 months (p<0.0005 for all). Patients in half-dose group had greater visual improvement at months 1 and 3 than those in the half-time group (p=0.004, and 0.026, respectively), but no significant difference at months 6 and 12. All eyes that received half-time PDT showed complete resolution of SRF within 6 months after PDT, but 3 eyes that received half-dose PDT had persistent SRF before loss to follow-up at months 5,7 and 8. Three of 32 eyes in the half-dose group and 2 of 26 eyes in the half-time group had recurrence of CSC during follow-up.

Author	Design	Population	Treatment	Follow-up (months)	Efficacy outcomes
Half-dose verteporfin					
Fujita K et al (35)	Retrospective case series	204 pts (204 eyes)	All half dose PDT	12	<ul style="list-style-type: none"> 182/204 eyes (89.2%) had complete resolution of the serous retinal detachment. Eleven eyes had a persistent SRD throughout the follow-up period, and 12 eyes had a recurrence of SRD after earlier resolution. Mean BCVA significantly improved from 0.11 ± 0.25 at baseline to 0.07±0.23 at 1 month, 0.02±0.23 at 3 months, 0.01±0.23 at 6 months, 0.00±0.24 at 9 months and -0.01 ±0.22 at 12 months (p<0.0001). No systemic complications or severe visual reduction reported
Tseng CC et al (36)	Retrospective case series	56 patients (56 eyes) Mean 45 years Symptoms of CSC for ≥3 months	All half dose PDT	55.5	<ul style="list-style-type: none"> Mean logMAR BCVA improved from 0.36 to 0.24 at 1 month and 0.13 at 6 months (both p<0.001) and remained stable thereafter. Four cases developed recurrence of SRF after one session of PDT Complications included enlargement of retinal pigment epithelial atrophy in one case and CNV in another two cases at 12 and 14 months after PDT.
Lai FH et al (37)	Retrospective case series	123 patients (136 eyes) Mean 49 years CSC for ≥ 3 months Presence of SRD involving the fovea	All half-dose PDT	57.7 ± 16.2	<ul style="list-style-type: none"> Complete resolution of SRD seen in 97.1% at 36 months with single PDT. Mean logMAR BCVA improved from 0.36 ± 0.29 at baseline to 0.15 ± 0.23 at 36 months (p<0.001). BCVA improved by 3 lines in 32.4% and reduced by 3 lines in 3.7% at 36 months 9 eyes (6.6%) had CSC recurrence; 5 retreated and 4 resolved spontaneously 5.9% had complications related to PDT
Nicolo M et al (38)	Retrospective case series	37 pts (38 eyes) Mean 48 years CSC for ≥6 months BCVA 20/200 or better	All half-dose PDT	14.2 ± 5.8	<ul style="list-style-type: none"> Dry macula was seen in 86.8% at 1 mo and 92.1% at end of follow-up There was a significant decrease in central FT BCVA improved by 3 lines in 39.5% and was unchanged in 57.8%; overall it improved significantly (from 0.74 0.19 ± to 0.83 ± 0.2; p=0.001) Cases with posterior cystoid retinal degeneration responded poorly
Zhuang (39)	Retrospective case series	36 pts (36 eyes)	All PDT	24 weeks	<ul style="list-style-type: none"> Complete SRF resolution in 36 eyes (75%) with no recurrence up to 24 weeks Mean BCVA improved from 0.52 to 0.80
Half-fluence PDT (standard dose verteporfin)					
Leys et al (26)	Retrospective review	34 pts (38 eyes)	Low-fluence PDT	43.97	<ul style="list-style-type: none"> Mean BCVA improved significantly from 0.33 to 0.11 at the last follow-up which corresponds to a gain of 2.2 lines At 3 months, complete resolution of central subretinal fluid was achieved on OCT after 1 PDT in 37 eyes and after 2 PDTs in 1 eye (retreated at 3 months after first PDT). One patient developed CNV 4 years after PDT and received anti- VEGF injections
Lim (27)	Prospective, non-comparative	30 pts (30 eyes), chronic CSC with symptoms for ≥6 mo No previous tmnt	All half-fluence PDT	6 months	<ul style="list-style-type: none"> LogMAR BCVA improved from 0.39 ± 0.21 at baseline to 0.18 ± 0.17 at 6 months (p<0.001). Improvements were seen regardless of the degree of hyperfluorescence (choroidal permeability) 17/30 patients overall had improvements in vision of 2 lines or more, and the remaining 13 eyes had stable vision
Ohkuma (28)	Retrospective case series	21 pts (22 eyes) Mean age 54 years (range 43-76 years)	All low-fluence PDT	12 months	<ul style="list-style-type: none"> BCVA significantly improved between 3 and 12 months: mean logMAR was 0.22 ± 0.31 baseline, 0.09 ±0.23 at 3 months, 0.08 ± 0.24 at 12 months The mean improvement was 1.5 lines at 12 months Six eyes (27.2%) had ≥2 lines improvement
Smretsching (29)	Retrospective case series	19 pts (20 eyes) Symptoms for ≥6 months	All low-fluence PDT	12 months	<ul style="list-style-type: none"> Mean BCVA improved from 40 to 44 letters (p<0.01) CFT decreased by a mean of 103 microns after 12 months Subretinal fluid resolved in 100% after one month Three eyes recurred and retreated within 12 months

FLP – focal laser photocoagulation; SRF – subretinal fluid; FT – foveal thickness, CMT = central macular thickness, CFT = central subfield foveal thickness

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**Bedfordshire and Luton Joint Prescribing Committee (JPC)
Assessment against Ethical and Commissioning Principles**

Treatment assessed (date): 28 June 2017

Photodynamic therapy (PDT) with verteporfin (Visudyne®) for chronic central serous retinopathy.

JPC Recommendation

- To support the use of PDT with verteporfin for the treatment of Chronic Central Serous Retinopathy.
- Approval is subject to patient outcomes being provided (via Blueteq reauthorisation process).

1) Clinical Effectiveness

There is an abundance of lower quality data available for PDT in the treatment of CSC and a handful of very small randomised controlled trials. Lower doses of verteporfin and lower fluence laser have been evaluated as a way of reducing potential complications and so the available studies feature a range of protocols.

Although the studies have been heterogeneous, they have overall consistently reported that PDT is associated with improvements in mean visual acuity (e.g. mean improvement of 0.23 logMAR with half-dose PDT and 0.19 logMAR with full-dose PDT in one small RCT) with resolution of CSC in all or almost all eyes treated. Although some patients have had disease recurrence (proportions reported have varied), retreatment has often been successful.

The available non-randomised studies/series comparing full and half-fluence PDT suggest broadly similar improvements in visual acuity; although there were some small differences noted they were not statistically significant (the studies were not designed or powered however to be able to detect such differences). Findings suggest half-fluence PDT is associated with less choroidal hypoperfusion but further, longer-term studies would be required to determine the clinical relevance of this.

One RCT found half-dose PDT to be associated with similar visual acuity improvements to full-dose PDT; although improvements were larger for the half-dose PDT the difference was not statistically significant (the study was small and power was limited). CSC resolution was seen in all eyes treated. There is an abundance of other lower quality, non-comparative data for half-dose PDT; the largest review reports a mean visual improvement of 1.8 lines and recurrence in 20%.

One prospective, randomised study has compared full-fluence to half-dose PDT and found both to be similarly effective in terms of improvements in visual acuity and resolution of subretinal fluid.

Other lower quality data are available suggesting similar outcomes for full versus half-dose PDT and full versus half-fluence PDT but the lack of randomised data means it is not possible to make any firm conclusions as to their relative efficacy and long-term safety. The optimal schedule (dose and fluence) remains to be determined.

Two pilot studies have compared low-fluence PDT to anti-VEGF agents (ranibizumab and bevacizumab); the mean change in visual acuity was similar but PDT was associated with a lower risk of recurrence.

There are no national guidelines on the management of this rare condition and currently no evidence-based consensus on its management. A recent Cochrane network meta-analysis concluded that overall the current evidence for any intervention for the treatment for CSC is low to very low; however that for PDT is 'somewhat stronger'.

2) Cost Effectiveness

NICE guidance discusses cost-effectiveness of verteporfin PDT for AMD
No separate cost-effectiveness studies for the other indications were found.

3) Equity None identified.
4) Needs of the community This is a rare condition. Prevalence is estimated at 5.8 per 100,000 but this includes cases that resolve spontaneously and also acute cases. LCCG has received 2 requests for verteporfin/PDT for the treatment of Chronic Central Serous Retinopathy in the last 2 years while BCCG has received no requests. (The last time that BCCG received a request was in 2012 when 5 requests had been received).
5) Need for healthcare (incorporates patient choice and exceptional need) There have been a variety of interventions used, or proposed for use, in CSC, including laser treatments, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents; medications that alter steroid hormones; and others. There is however at present no evidence-based consensus on its management. Laser photocoagulation can only be used where the treatment area is well defined and cannot be used in the centre of the fovea due to concerns of incidental damage.
6) Policy drivers None identified
7) Disinvestment

The JPC agreed the following sections within the PCT Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table

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