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**Statement of the German Ophthalmological Society,
the Retinological Society and
the Association of Ophthalmologists in Germany**

**on current therapeutic options
in neovascular age-related macular degeneration**

June 2007



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Introduction and preliminary remarks

Basic conditions in the treatment of exudative AMD¹ have changed substantially since the last statement of the professional societies [1]. After the registration of pegaptanib for intraocular treatment of AMD, ranibizumab has also been approved in Germany since February 2007. In addition, the quality assurance agreement on fundus photodynamic therapy has been amended, whereby new provisions were included for the treatment of occult CNV [2] and the proposal of the societies for a more precise nomenclature of subfoveal and extrafoveal CNVs [1] [3] was followed. It was therefore necessary to adapt the societies' recommendations for the treatment of AMD to take account of these changes in the situation.

Treatment principles

Photodynamic therapy with verteporfin

Photodynamic therapy (PDT) with verteporfin has been the subject of several detailed prospective studies in various subtypes of exudative subfoveal AMD. The principle of treatment and the indications of subfoveal, predominantly classic CNV and occult CNV with proven disease progression (associated subretinal hemorrhage or documented progressive loss of visual acuity or increase in lesion size), as demonstrated in Phase III studies, have already been described [1, 4]. However, according to a recommendation of the EMEA Committee for Medicinal Products for Human Use of May 2007, it has to be assumed that EMEA approval of verteporfin for occult CNV will be revoked, because efficacy has not been demonstrated in a confirmatory Phase III study (VIO study) [5].

The effect of PDT must be assessed by fluorescence angiography after about two or three months to decide whether the PDT should be continued. If staining persists or there is renewed rapid staining of CNV with leakage and/or increase in lesion size or further loss of visual acuity, it is a good idea to repeat PDT or, if necessary, to administer intravitreal medical therapy (see below). On the other hand, if there is no leakage (only staining of the CNV) it is possible to forego repeat PDT for the time being. In comparison with other treatments, PDT is the least complicated procedure and is also the procedure with which the longest experience has been gained in clinical studies and in everyday clinical practice. In Germany, moreover, funding for this therapy has been accepted in the health insurance system for subfoveal, predominantly classic CNV.

Monotherapy with triamcinolone

No unequivocal therapeutic effect has been demonstrated either in prospective randomized studies or in retrospective studies. The initial effect detectable after 3 months is no longer discernible after 12 months [6]. Since specific side effects, such as an increase in intraocular pressure, progression of cataract and a risk of endophthalmitis, also occur with the intravitreal injection of triamcinolone, monotherapy with triamcinolone for the treatment of neovascular AMD is not a good idea [7-9].

Anecortave acetate

Anecortave acetate is a steroid modification which primarily inhibits angiogenesis and shows none of the glucocorticoid activity which is largely responsible for the increase in pressure. Anecortave acetate is injected into the eyeball. The duration of action is longer than with triamcinolone. Recent studies have shown that anecortave acetate has an effect similar to that of PDT in the treatment of predominantly classic CNVs [10, 11]. However, this product is not registered in Germany.

VEGF inhibitors

Pegaptanib

The therapeutic principle and the studies carried out to date (V.I.S.I.O.N studies EOP1003 and EOP1004) have already been presented [4, 12, 13]. Although the substance was registered in the USA back in December 2004, the data remains substantially unchanged since the last statement [1]. The value of monotherapy with pegaptanib rests essentially on the results of the V.I.S.I.O.N studies, whose 2-year results

¹ A glossary of the abbreviations used can be found at the end of the text



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after re-randomization were published in 2006 [14]. These showed that a therapeutic effect could only be maintained among patients in whom intravitreal therapy with pegaptanib (one injection every 6 weeks) was continued over two years. Patients in whom intravitreal therapy with pegaptanib was discontinued after one year did not have any advantage over patients who received sham injections. No further prospective Phase III studies are available on monotherapy with pegaptanib. At the present time, it is not yet possible to assess the extent to which the combination of pegaptanib with other VEGF inhibitors offers better results [15].

Ranibizumab

Ranibizumab is a recombinant, monoclonal antibody fragment that shows a high binding affinity for VEGF-A and its isoforms. This hinders activation of the signal cascade via the various VEGF receptors. By means of this molecular mechanism, ranibizumab inhibits the formation of new vessels and their hyperpermeability and can thus exert a beneficial effect on CNV-induced macular edema.

In the meantime, 12 and 24-month data are available from two Phase III studies, which were published at the end of 2006 and involved about 1200 patients [16, 17]. In these studies, ranibizumab was administered by intravitreal injection at 4-week intervals.

According to data from the MARINA study in 716 patients with minimal classic or occult CNV, more than 90% of patients treated with ranibizumab showed a reduced visual acuity of less than 3 lines on the ETDRS chart, both after 12 months and also after 24 months. After one year, the patients treated with 0.5 mg ranibizumab showed a mean visual acuity gain of 7.2 letters (a gain of 5 letters corresponds to a visual acuity gain of 1 line), whereas the sham injection group showed a decline in visual acuity of 10.4 letters.

According to data from the ANCHOR study in 423 patients with predominantly classic CNV, about 95% of patients treated with ranibizumab likewise showed that visual acuity was reduced by less than 3 lines after 12 months of therapy compared with only 64% of patients who showed the same effect during photodynamic therapy (PDT) with Visudyne. In this study, the mean visual acuity gain after one year amounted to 11.3 letters on the ETDRS chart (0.5 mg ranibizumab) versus a mean loss of 9.5 letters in the group of patients treated with verteporfin (PDT).

In January 2007, ranibizumab was approved in the dose of 0.5 mg per injection for the treatment of neovascular AMD. In contrast to American treatment recommendations with monthly injection of ranibizumab, the recommendation in the summary of product characteristics for the European registration (based on a mathematical model) is for an initial loading phase of three monthly injections followed by maintenance therapy based on the results of individual monitoring for visual acuity [18]. However, the results of the PIERS study, which have not yet been published, have shown that a general increase in the intervals between injections results in a mean loss of vision, so it can be assumed that most cases require more than 3 monthly injections.

The controlled clinical trials submitted in the registration dossier did not show any evidence to suggest systemic side effects of ranibizumab. In a Phase III b study (SAILOR; 0.3 mg vs. 0.5 mg ranibizumab), which was only carried out in the USA, an interim analysis was performed after 6 months in the first cohort of patients. This showed a difference between the two treatment arms with regard to the frequency of stroke. This difference was significant (1.2% vs. 0.3%; $p=0.02$) after 6 months, but not after 9 months [19]. In a statement by the FDA in February 2007, it was noted that the incidence of stroke in both dose arms of the SAILOR study was lower than in the controlled clinical trials. The FDA did not see any need to change the approved dose, or to include a corresponding note in the prescribing information with regard to a special risk. This assessment arises from a comparison of the incidence of stroke in the age group for which AMD is typical with the incidence of stroke in the treatment arms of the controlled clinical trials of ranibizumab [20].

Bevacizumab

The active principle and structural properties of the whole antibody have already been presented [1]. In the meantime, it has been demonstrated that, after intravitreal injection, the relatively large molecule (148 kDa compared with 48 kDa in the case of ranibizumab) completely penetrates the retina and the choroid in primates [21]. For the time being, however, the way in which its overlapping binding epitopes and lower binding affinity impact on biological efficacy remains unclear. In cell culture, no statistically significant differences were found between pegaptanib, ranibizumab and bevacizumab with regard to their effect on the



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growth activity of the vascular endothelium of the choroid (in pigs) [22]. Current electrophysiological studies show that there is a recovery of the photoreceptors during treatment with bevacizumab even in the region of the neovascular membrane [23]. The undiluted stock solution (25 mg/mL) can be used for the injection. Prolonged storage of the frozen active substance should be avoided, because this has been shown to affect the concentration and biological activity over time [24]. Refrigerated storage and maintenance of the refrigeration chain during transport is therefore important [25].

Possible advantages of bevacizumab over ranibizumab consist in the longer half-life and greater stability of the molecule, which in theory promise longer treatment intervals and thus a lower frequency of repeat treatments. However, until we have data from a prospective, randomized, head-to-head study comparing the safety and efficacy of bevacizumab and ranibizumab, it is not possible to make a definitive assessment of any potential difference.

Data on the efficacy of bevacizumab in AMD are only available to date for relatively short observation periods and without any control groups [26]. Here, the positive results are comparable overall with the scale of improvement in visual acuity reported in the MARINA and ANCHOR studies in the first few months after the administration of ranibizumab [27, 28]. As far as it is possible to assess on the basis of small case series, there is no evidence to suggest any notable differences in effect between different angiographic membrane types [29].

Bevacizumab is not approved either for intravitreal administration or for treatment of AMD. There has not yet been any standardized and controlled recording of systemic side effects [30]. In particular, therefore, it is unclear whether repeated use carries an increased risk for thromboembolic events. Observations of biological effects in the contralateral eye indicate that the systemic concentration can induce relevant changes in tissues outside the original site of administration [30, 31]. There is no evidence as yet to suggest that the expected systemic complications are any greater than with the intravitreal administration of ranibizumab [32, 33]).

In terms of local side effects, bevacizumab would not appear to differ from other medicines. The risk of infection after intravitreal injection is no greater than that of other VEGF inhibitors [34]. Intraocular irritation has only very rarely been observed. Lesions in the pigment epithelium have been observed in particular during the treatment of extensive pigment epithelium detachment [35, 36].

Combinations

PDT + intravitreal triamcinolone

Photodynamic therapy (PDT) may be supplemented by combining it with intravitreal injection of triamcinolone. In such cases, triamcinolone is injected a few days before or immediately after PDT. The intravitreal use of this steroid is intended to limit both the inflammatory reactions that set in after PDT and also any increase in VEGF production. The usual dose administered is 4 mg triamcinolone in 0.1 mL [37, 38], but higher doses up to 25 mg have been used [39]. The essential therapeutic effect of this combination therapy appears to lie in a lower number of the PDT sessions needed to achieve CNV scarring. It remains open to question whether a positive influence on visual acuity is possible in terms of less loss of visual acuity or even more frequent improvements in visual acuity, because clinical experience to date is based only on sizeable case series, in some cases with an inhomogeneous mix of different subtypes of neovascular AMD, thus making it impossible to compare results directly with those of clinical Phase III studies of PDT and anti-VEGF treatments [37-40].

Moreover, a not inconsiderable profile of side effects has been documented in all case series. In addition to the risk of endophthalmitis [41] and the progression of cataract, which is almost always observed, one effect that has been described in particular is an increase of intraocular pressure in about 25% of patients, which in some cases persisted for a long time [37-40, 42, 43]. It would therefore seem a good idea at present not to combine PDT and intravitreal triamcinolone injection, except in exceptional cases, especially since other effective treatments are available (see below).



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Triple therapy

Some authors have recommended combining three therapeutic procedures in the treatment of exudative AMD. These have included the combination of PDT, intravitreal triamcinolone and pegaptanib [44] and also the combination of PDT, intravitreal dexamethasone and intraocular bevacizumab [45]. To date, however, only case-control studies without the use of controls have been published, and although these have described a positive effect and better results than one procedure alone, their results have not been confirmed by a controlled study.

Future options

The inhibition of growth factor VEGF undoubtedly represents only the first step in the new era of anti-angiogenesis as a therapeutic principle for treating neovascular AMD. Today a new and growing arsenal of substances from a range of different classes is already undergoing preclinical and clinical studies. Although VEGF is not always the primary site of action, inhibition or modulation of the cascade induced by VEGF, amongst other factors, plays a contributory role.

The signal chain may be inhibited at a variety of sites. The substances known to us, i.e. pegaptanib, ranibizumab and bevacizumab, sequester the VEGF-A isoforms and thus prevent binding to the corresponding receptor ligands. Another active principle is the blockade of receptors, e.g. by antibodies, or of the downstream intracellular cascade, e.g. by tyrosine kinase inhibitors. The signal chain may also be inhibited at its source by transcription-inhibiting molecules, e.g. by 'short interfering (si)' RNA [46]. Thanks to the lack of protein expression, this principle is also known as 'gene silencing'.

The angiostatic substances currently being tested, especially in oncology, are almost countless in number. Translation from the laboratory to clinical use depends partly on their effectiveness in inhibiting angiogenic processes *in vitro* and *in vivo*, but also on their risk profile vis-à-vis physiological mechanisms. Despite the justified enthusiasm surrounding the new treatment options, there has to be greater awareness of the fact that there is a major interference not only in pathological processes, but also in physiological processes and structures. Although VEGF represents an essential factor in neovascular diseases and AMD, animal experiments unequivocally show that blocking this factor also exerts negative influences on physiological vessels, on glomerular endothelial cells and on pulmonary alveolar endothelial cells, and also leads to neuronal disturbances with corresponding functional deficits (see [47] for overview). It has to be expected that chronic use of the current anti-VEGF treatments is necessary in most patients for their intervention in the signal chain and not in the cause of the disease. The value of new forms of treatment will therefore also depend substantially on the systemic risk profile.

Recommendations

Diagnosis

A test of visual acuity (best corrected VA with normal pupils under standardized conditions) and clinical fundus examination (biomicroscopic examination of the posterior pole of the eye with mydriasis) are the basis of all therapy. Fluorescein angiography remains the gold standard for establishing the diagnosis and is necessary with all first-time treatments and thereafter at least before the 4th injection therapy and in the further clinical course if the disease progresses. Optical coherence tomography (OCT) can be a useful adjunct, but is not sufficient on its own. Differentiation according to localization (subfoveal or non-subfoveal), lesion size (smaller/larger than 4 MPS disk areas) and angiographic pattern (predominantly classic CNV, minimal classic CNV, occult CNV and other features such as RAP), which is relevant e.g. for the prognosis, is only possible by fluorescein angiography. It has to be borne in mind that, even with angiography, unequivocal classification is not always possible and further treatment criteria, such as residual function (best corrected visual acuity at least 0.05), development of the clinical finding ('*recent disease progression*': proven reduction in visual acuity, growth in lesion size or subretinal hemorrhage) and function of the contralateral eye, must be taken into account when establishing the diagnosis. Future therapeutic strategies may possibly attach priority to additional criteria such as lesion size.



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Therapy

Differential indication – ‘first line’ and ‘second line’ therapy

The studies at the root of this work were assessed on the basis of the Oxford scale criteria [48]. Financial aspects were not considered when assessing the indications. With regard to the legal and medical problems of so-called off-label use, reference is made to the literature [49, 50]. On this basis, the following recommendations emerge:

Extrafoveal CNV

For classic CNV without occult CNV outside the avascular zone of the fovea, thermal laser coagulation is the only treatment option to have been studied to date in Phase III studies. In long-term use (5 years) this treatment can lower the risk of a further loss of visual acuity from 80% if untreated to 60% when treated [51]. However, the efficacy of PDT in extrafoveal predominantly classic CNV has only been shown to date in case series [52], and the results were not unequivocally better than established treatment procedures. But the angiographic differentiation of CNV, which has been developed further in recent years, has shown that extrafoveal membranes can occur with occult subfoveal CNV. This may therefore be a meaningful indication for intravitreal injection of a VEGF inhibitor, which is also covered by the registration of ranibizumab in the treatment of exudative AMD.

Subfoveal CNV

The problems of comparing different studies was already discussed in the last statement [1]. The difference in results between the treatment and control groups in each case appears most conclusive for comparing the effectiveness of individual studies. If the comparison is based on inclusion criteria, the stated differential figures for stabilization or improvement in visual acuity and the above-mentioned criteria of assessment, ranibizumab represents *first-line* therapy for the various types of exudative AMD studied (visual acuity greater than/equal to 0.05 in predominantly classic CNV, minimally classic CNV and occult CNV with proven disease progression). With regard both to the functional stabilization effects (about 95% in all types) and also to the possibility of an improvement in visual acuity (about 30% in all types), ranibizumab showed the best results. However, the above results were obtained in studies which envisaged a 4-week administration of ranibizumab over a period of 2 years (24 intravitreal injections). Since further injections were also needed by about 40% of these study patients in the 3rd year as well, the patient and treating physician must be aware at the start of treatment that long-lasting injection therapy may be necessary. Both this and a lack of response to treatment with ranibizumab may make the use of PDT or intraocular therapy with pegaptanib appear a good idea (*second-line* therapy).

Owing to the identical active principle of bevacizumab, the intravitreal injection of this substance represents a rational treatment alternative that has now been underpinned by numerous reports despite its status of *off-label* use and the absence of Phase III study results on safety and efficacy with bevacizumab.

One aspect which all intravitreal medicines have in common is the risk of endophthalmitis associated with intravitreal injection, which can rise to a cumulative risk of 2% per year with monthly injections administered in conformity with protocol. It is therefore only possible on a case-by-case basis to weigh the risk of intravitreal therapy against the potential benefit in terms of a possible stabilization of visual acuity.

The combination of intravitreal VEGF inhibitors with PDT is not recommended as primary therapy, because it has not been proved to be more effective than monotherapy. For the time being, the clinical studies that are still ongoing should be awaited. But this combination might already offer an additional treatment option in those cases where the individual treatments alone are not effective enough. Moreover, the combination of intravitreal VEGF inhibitors with pars plana vitrectomy is rejected because there is no evidence to suggest that this is more effective than intravitreal injection with VEGF inhibitors alone, the half-life of the administered medicine is shortened after vitrectomy and the markedly greater risks of pars plana vitrectomy have to be taken into account.

The extent to which treatment with bevacizumab in combination with other methods offers advantages in terms of efficacy and prolonged treatment intervals remains to be seen [53]. For ethical reasons, therefore,



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patients whose costs for standard therapeutic agents are not (yet) covered and who cannot afford to cover the costs themselves should continue to be referred for treatment with intravitreal bevacizumab. In these cases, patients should be made aware of the 'off-label use' and of the existence of an approved product for the same indication, and the treating physicians should consider the legal consequences, including product liability, also in relation to unknown side effects [49].

Pigment epithelium detachment

At present, there is no therapeutic procedure that has been established in Phase III studies for occult CNV or retinal angiomatous proliferations (RAP) associated with detachment of the retinal pigment epithelium [54]. Both thermal laser coagulation and also PDT monotherapy were associated with pigment epithelium tears and recurrences of CNV, as a result of which there was no improvement in the natural history. Both the combination of PDT with triamcinolone and treatment with VEGF inhibitors (especially Avastin) led to a flattening of the detached pigment epithelium and a stabilization of visual acuity in case series [55-58]. In these series, however, the occurrence of pigment epithelium tears was also reported in about 15-25% of patients, but these were mostly extrafoveal and, without any recurrence of CNV, had hardly any negative consequences on visual acuity [36, 59]. In view of the known side effects profile of the combination PDT plus triamcinolone (see above), anti-VEGF therapy seems the most sensible option at present, although differing therapeutic efficacy of the different anti-VEGF substances would seem a possibility. Moreover, a continuation of therapy must be considered if pigment epithelium tears occur, because the continued growth of CNV in these cases is accompanied by rapidly progressive loss of visual acuity.

Follow-up studies, treatment frequency and intervals

Follow-up

For follow-up, the visual acuity (under standardized conditions, best corrected, with normal pupils) and fundus (biomicroscopic examination of the posterior pole of the eye with mydriasis) should be tested at least before each treatment and during the first six months after the end of treatment about every 4 to 8 weeks depending on the medicine used and the clinical course. These tests are also necessary whenever there is a subjective deterioration. Fluorescein angiography should be repeated at least before the 4th injection treatment and in the further clinical course as the disease progresses. This makes sense in order to keep track of the morphological changes during therapy, the indication for continuation of therapy and any change in the findings. It should be explained to the patients that they should attend for a check-up as soon as possible if they note a subjective worsening of their condition.

Future therapeutic strategies may possibly attach greater priority to other criteria, such as lesion size. But since all study plans and efficacy statements to date refer to the existing angiographic classification of exudative AMD, this continues to be relevant for comparing the efficacy of the different approaches to treatment.

Treatment frequency, treatment intervals, repeat therapy:

In the prescribing information for ranibizumab, an initial regimen of 3 intravitreal injections at 4-week intervals is recommended (loading dose). In a minority of patients, a single injection series is sufficient to achieve stabilization of visual acuity for one year. In the other patients, the frequency of repeat therapy has to depend on the clinical course and individual experiences. In patients who show marked worsening despite a reloading dose, treatment should not be continued any longer or there should be a change of treatment.

On the basis of the study results, the effectiveness of this approach lends itself to the interpretation that a response to therapy can be 'tested' in this way because all the stabilization and improvement in visual acuity were discernible after the first injections. But this does not mean that further injections may not be necessary. Indeed, in view of the fact that, even after 2 years of treatment with ranibizumab injections every 4 weeks, further growth of CNV and further need for treatment were observed in about 40% of study patients, it has to be concluded that longer-lasting injection therapy is necessary in numerous patients. However, after the loading dose of 3 intravitreal injections of ranibizumab, the individual treatment interval needed may be estimated based on check-ups every 4 weeks, because it has been shown in clinical studies



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that some patients needed further injections at 4-week intervals to achieve therapeutic success, while others showed similar results with injections at 3-month intervals.

For this reason, if the response to treatment after the 3rd injection is initially positive, then further treatments should be administered if the check-ups and control fluorescein angiography show evidence of disease progression (visual acuity poorer, new hemorrhage(s) in the macula, increase or reactivation of macular edema and/or of CNV) and the criteria for ending treatment are not met.

Change of treatment

If there is a lack of response to therapy, a change in the form of treatment may be a good idea provided the following criteria for ending therapy are not met.

End of therapy and discontinuation of therapy

According to the therapeutic principle described above, end of treatment can only be accepted if, after the withdrawal of therapy, the defined criteria for further treatment and disease progression (visual acuity poorer, new hemorrhage in the macula, increase in macular edema, progression or reactivation of the exudative lesions in the fluorescein angiogram) are no longer met. Although there are currently no data on how long intravitreal injections have to be continued for any anti-VEGF treatments, further treatment would likewise appear not to be a good idea if visual acuity falls below 0.05, or if there is extensive subretinal fibrosis or atrophy. A discontinuation of therapy should also be considered if it appears unlikely that a further loss of visual acuity can be halted with treatment and thus no further beneficial effect is to be expected on the patient's quality of life. This is essentially the case if the disease has entered its morphological and functional end-stage.

In the case of treatment with PDT, it remains the case that further treatment is not necessary if the check-up shows stable findings, biomicroscopy reveals a fibrovascular scar with or without minimal subretinal fluid and as far as possible no further fluorescein leakage from the CNV is discernible ('staining'). To monitor the stability of this situation, however, a further clinical check-up is advisable in 3 months. Moreover, PDT therapy should be ended or discontinued if visual acuity has fallen below 0.05 and, despite PDT, there has been further marked growth of CNV. It is also advisable not to give any further PDT therapy if there is extensive subretinal hemorrhage.

Treatment procedure

As a rule, all injection therapy and PDT are administered on an outpatient basis. In individual cases, there may be a medical need for inpatient treatment (e.g. reduced general condition, only one functional eye, lack of care at home on the day of injection).

As regards the practical aspects of treatment, it is also essential to note that intravitreal injection is a surgical, intraocular procedure which is subject to the same conditions in terms of care, safety, patient guidance, minimization of risk and post-operative monitoring as with any other intraocular procedure, e.g. in cataract surgery. For this reason, the surgical conditions of intraocular injection correspond to those of cataract surgery. There are no evidence-based data [61] to support preoperative prophylaxis with topical antibiotics as demanded by some authors [60] and in prescribing information for Lucentis® [18], which means such a procedure is at the discretion of the surgeon. An ophthalmological check-up with split-lamp examination, measurement of intraocular pressure and examination of the fundus should be carried out on the first to fourth post-operative day after intravitreal injection.

Glossary

Abbreviations used:

AMD: Age-related macular degeneration

CNV: Choroidal neovascularization

EMA: European Agency for the Evaluation of Medicinal Products

ETDRS: Early Treatment of Diabetic Retinopathy Study

FDA: Food and Drug Administration (USA)



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GKV: *Gesetzliche Krankenversicherung* (legally required health insurance in Germany)

MPS: Macular photocoagulation study

OCT: Optical coherence tomography

PDT: Photodynamic therapy

RAP: Retinal angiomatous proliferation

VEGF. Vascular endothelial growth factor

Trade names:

Pegaptanib: Macugen® (Pfizer Ophthalmics)

Verteporfin: Visudyne® (Novartis Ophthalmics)

Ranibizumab: Lucentis® (Novartis Ophthalmics)

Bevacizumab: Avastin® (Roche)

Anecortave acetate: Retaane® (Alcon Inc.)

Editorial note²

Financial disclosure according to the following system:

F: Financial sponsorship by a company in the form of participation in a study (FSt-n), research projects (FFp-n-x), other (Fs) (n: indicates the number of studies or research projects) (x: indicates the volume. X: €0 – 50,000, XL: €50,000 – 100,000, XLL: > €100,000)

P: Personal financial interest, shares, funds of over €30,000 in a company

A: Employee of a company that markets the product or a competitor product.

B: Consultant for company during the last three years (consultancy agreement)

P: Patent holder, share of patent, license holder of a company product, etc.

K: Cost reimbursement, fee, invitation to lectures

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² The members of the Macula Commission can be found at
<http://www.dog.org/dog/kommissionen.html#Makula>



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