ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Macugen 0.3 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe provides a usable amount to deliver a single dose of 90 microlitres containing pegaptanib sodium, corresponding to 0.3 mg of the free acid form of the oligonucleotide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
The solution is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Macugen is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) in adults (see section 5.1).

4.2 Posology and method of administration

Macugen should only be administered by ophthalmologists experienced in intravitreal injections.

Posology
The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section 4.4).

The recommended dose is 0.3 mg pegaptanib, equivalent to 90 microliters, administered once every six weeks (9 injections per year) by intravitreal injection into the affected eye.

Following the injection, transient increases in intraocular pressure were seen in Macugen treated patients. Therefore, the perfusion of the optic nerve head and intraocular pressure should be monitored. Moreover patients should be closely monitored for vitreous haemorrhage and endophthalmitis in the two weeks following the injection. Patients should be instructed to report any symptoms suggestive of these conditions without delay (see section 4.4).

After 2 consecutive injections of Macugen, if a patient does not demonstrate a treatment benefit (loss of less than 15 letters of visual acuity) at the 12-week visit, consideration should be given to stopping or withholding Macugen therapy.

Special populations

Elderly
No special considerations are needed.

Hepatic impairment
Macugen has not been studied in patients with hepatic impairment.
However, no special considerations are needed in this population (see section 5.2)

Renal impairment
Macugen has not been adequately studied in patients with severe renal impairment. Dose adjustments are not recommended in patients with mild or moderate renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of Macugen in children under 18 years has not yet been established. No data are available.

Method of administration
For intravitreal injection use only.

Macugen should be inspected visually for particulate matter and discoloration prior to administration (see section 6.6).

The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). Adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection.

The pre-filled syringe is supplied with an excess product volume. Injecting the entire volume of the prefilled syringe could result in overdose (see section 4.8 and 4.9). See section 6.6 for instructions to expel the excess volume before injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active or suspected ocular or periocular infection.

4.4 Special warnings and precautions for use

Endophtalmitis
Intravitreal injection procedures are associated with a risk of endophthalmitis; in Macugen clinical trials, the incidence of endophthalmitis was 0.1% per injection (see section 4.2).

Increased intraocular pressure
As expected with intravitreal injections, transient increases in intraocular pressure may be seen. Therefore, the perfusion of the optic nerve head should be verified and elevation of intraocular pressure should be managed appropriately post injection.

A post marketing observational study has also reported on a small risk of slow sustained increase in intraocular pressure (see section 4.8).

Intravitreous haemorrhages
Immediate (on the day of injection) and delayed intravitreous haemorrhages may occur following pegaptanib injections (see section 4.2).

Hypersensitivity reactions
Cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been observed within several hours after the pegaptanib intravitreal administration procedure in the post-marketing experience. A direct relationship to Macugen or any of the various treatments administered as part of the injection preparation procedure, or to other factors has not been established in these cases.

Systemic effects

Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in patients with prior history of stroke or transient ischaemic attacks. Caution should be exercised when treating such patients (see section 4.8, heading 'Product-class-related adverse reactions').

Overfill volume
Injection of the entire volume of the pre-filled syringe could result in serious adverse events; therefore, the excess volume must be expelled before injection (see sections 4.8 and 6.6).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interaction studies have not been conducted with Macugen. Pegaptanib is metabolised by nucleases and therefore cytochrome P450 mediated drug interactions are unlikely.

Two early clinical studies conducted in patients who received Macugen alone and in combination with PDT (photodynamic therapy) revealed no apparent difference in the plasma pharmacokinetics of pegaptanib.

4.6 Fertility, pregnancy and lactation

Pregnancy
Pegaptanib has not been studied in pregnant women. Animal studies are insufficient, but have shown reproductive toxicity at high systemic exposure levels (see section 5.3). The potential risk to humans is unknown. The systemic exposure to pegaptanib is expected to be very low after ocular administration. Nevertheless, Macugen should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Breast-feeding
It is not known whether Macugen is excreted in human milk. Macugen is not recommended during breast-feeding.

Fertility
No human data on the effect of Macugen on fertility are available. In animal studies no effects on male or female fertility in mice were observed. See section 5.3.

4.7 Effects on ability to drive and use machines

Macugen has a minor influence on the ability to drive and use machines due to the possible temporary visual blurring after administration of Macugen by intravitreal injection. Patients should be instructed not to drive or use machines until this has resolved.

4.8 Undesirable effects

Summary of the safety profile
The majority of adverse reactions reported following administration of Macugen are related to the intravitreal injection procedure.

In clinical trials the most frequently reported ocular adverse reactions following injection of Macugen are: anterior chamber inflammation, eye pain, increased intraocular pressure, punctate keratitis,

vitreous floaters and vitreous opacities. Less frequently reported serious ocular adverse reactions included endophthalmitis, retinal haemorrhage, vitreous haemorrhage and retinal detachment.

Tabulated list of adverse reactions

The safety data described below summarise all procedure and adverse reactions in the 295 patients in the 0.3 mg treatment group. The adverse reactions are listed by system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and not known (cannot be estimated from the available data).

Reports from post-marketing experience are included in italics.

MedDRA system organ class	Adverse reaction
Immune system disorders	
Not known	*anaphylactic reaction**
Psychiatric disorders	
Uncommon	nightmare, depression
Nervous system disorders	
Common	headache
Eye disorders	
Very common	anterior chamber inflammation, eye pain, increased intraocular pressure, punctate keratitis, vitreous floaters and vitreous opacities
Common	abnormal sensation in eye, cataract, conjunctival haemorrhage, conjunctival hyperaemia, conjunctival oedema, conjunctivitis, corneal dystrophy, corneal epithelium defect, corneal epithelium disorder, corneal oedema, dry eye, endophthalmitis, eye discharge, eye inflammation, eye irritation, eye pruritus, eye redness, eye swelling, eyelid oedema, lacrimation increased, macular degeneration, mydriasis, ocular discomfort, ocular hypertension, periorbital haematoma, photophobia, photopsia, retinal haemorrhage, vision blurred, visual acuity reduced, visual disturbance, vitreous detachment, and vitreous disorder
Uncommon	asthenopia, blepharitis, conjunctivitis allergic, corneal deposits, eye haemorrhage, eyelids pruritus, keratitis, vitreous haemorrhage, pupillary reflex impaired, corneal abrasion, retinal exudates, eyelid ptosis, retinal scar, chalazion, corneal erosion, decreased intraocular pressure, injection site reaction, injection site vesicles, retinal detachment, corneal disorder, retinal artery occlusion, retinal tear, ectropion, eye movement disorder, eyelid irritation, hyphaema, pupillary disorder, iris disorder, ocular icterus, anterior uveitis, deposit eye, iritis, optic nerve cupping, pupillary deformity, retinal vein occlusion, and vitreous prolapse
Ear and labyrinth disorders	
Uncommon	deafness, Meniere's disease aggravated, vertigo
Cardiac disorders	
Uncommon	palpitations
Vascular disorders	

Uncommon	hypertension, aortic aneurysm
Respiratory, thoracic and mediastinal disorders	
Common	rhinorrhea
Uncommon	nasopharyngitis
Gastrointestinal disorders	
Uncommon	vomiting, dyspepsia
Skin and subcutaneous tissue disorders	
Uncommon	contact dermatitis, eczema, hair colour changes, rash, pruritus, night sweats
Not known	*angioedema**
Musculoskeletal and connective tissue disorders	
Uncommon	back pain
General disorders and administration site conditions	
Uncommon	fatigue, rigors, tenderness, chest pain, influenza like illness
Investigations	
Uncommon	increased gamma-glutamyltransferase activity
Injury, poisoning and procedural complications	
Uncommon	abrasion

* Post-marketing experience; see "Description of selected adverse reactions"

Description of selected adverse reactions

Cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in patients within several hours after administration of pegaptanib along with various medicinal products administered as part of the injection preparation procedure (see sections 4.2 and 4.4).

Cases of serious increase in intraocular pressure have been reported when the excess volume in the pre-filled syringe was not expelled before injection.

Sustained small increases in intraocular pressure (IOP) have also been reported after repeated intravitreal dosing in a post marketing observational study. The odds of increased IOP was increased by a factor of 1.128 for each additional injection (p= 0.0003). No statistical difference was found in the incidence of increased IOP between patients with a history of increased IOP or glaucoma versus patients without.

Product-class-related adverse reactions

In the clinical trial, the overall frequency of non-ocular haemorrhages, an adverse event potentially related to systemic VEGF (vascular endothelial growth factor) inhibition, was slightly increased in intravitreal VEGF inhibitor-treated patients. However, there was no consistent pattern among the different haemorrhages. Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic including stroke and myocardial infarction events following intravitreal use of VEGF inhibitors.

A few cases of arterial thromboembolic events were observed in the pegaptanib clinical trials in patients with AMD, DME, and there were no major differences between the groups treated with pegaptanib compared to control.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose with Macugen has not been reported in clinical trials.

Overdosing with increased injection volume (e.g. when the excess volume in the pre-filled syringe is not expelled before injection) may elevate intraocular pressure (see section 4.8). Treating physician should always expel excess volume of solution according to instructions under the section 6.6. Therefore, in case of overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Ocular vascular disorder agents, ATC Code S01LA03.

Mechanism of action
Pegaptanib is a pegylated modified oligonucleotide that binds with high specificity and affinity to extracellular Vascular Endothelial Growth Factor ($VEGF_{165}$) inhibiting its activity. VEGF is a secreted protein that induces angiogenesis, vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of AMD.

Pharmacodynamic effects
$VEGF_{165}$ is the VEGF isoform preferentially involved in pathological ocular neovascularisation. The selective inhibition in animals with pegaptanib proved as effective at suppressing pathological neovascularisation as pan-VEGF inhibition, however pegaptanib spared the normal vasculature whereas pan-VEGF inhibition did not.

Reductions in the growth of mean total lesion size, choroidal neovascularisation (CNV size), and fluorescein leak size, have been shown in patients with AMD treated with Macugen.

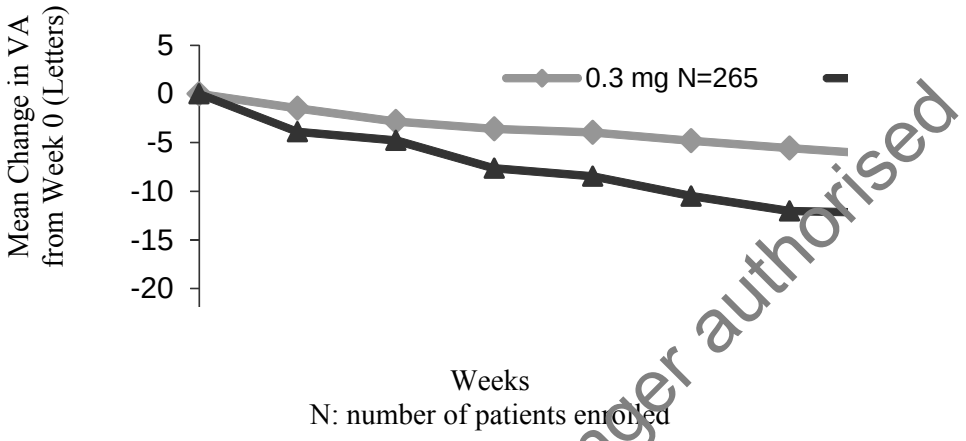
Clinical efficacy and safety
Pegaptanib was studied in two controlled, double-masked, and identically designed randomised studies (EOP1003; EOP1004) in patients with neovascular AMD. A total of 1190 patients were treated (892 pegaptanib, 298 sham (control)) with a median age of 77 years. Patients received a mean of between 8.4-8.6 treatments out of possible 9 total across all treatment arms in the first year.

Patients were randomised to receive sham or 0.3 mg, 1 mg or 3 mg pegaptanib administered as intravitreal injections every 6 weeks for 48 weeks. Verteporfin photodynamic therapy (PDT) was permitted in patients with predominantly classic lesions at the discretion of the investigators.

The two trials enrolled patients, including all neovascular AMD lesion subtypes (25% predominantly classic, 39% occult with no classic and 36% minimally classic), lesion sizes up to 12 disc areas, of which up to 50% could be comprised of subretinal haemorrhage and/or up to 25% fibrotic scar or atrophic damage. Patients had up to one prior PDT and baseline visual acuity in the study eye between 20/40 and 20/320.

At one year, pegaptanib 0.3 mg exhibited a statistically significant treatment benefit for the primary efficacy endpoint; proportion of patients losing less than 15 letters of visual acuity (prespecified pooled analysis, pegaptanib 0.3 mg 70% versus Sham 55%, p = 0.0001; EOP1003 pegaptanib 0.3 mg 73% versus Sham 59%, p = 0.0105; EOP1004 pegaptanib 0.3 mg 67% versus Sham 52%, p = 0.0031).

Mean Change in Visual Acuity Over Time; Year 1; ITT (LOCF)



Pegaptanib 0.3 mg showed treatment benefit regardless of baseline lesion subtype, lesion size and visual acuity as well as age, gender, iris pigmentation and prior and/or baseline PDT usage.

At the end of the first year (week 54), 1053 patients were re-randomized to either continue or discontinue treatment through week 102.

On average, the treatment benefit was maintained at 102 weeks with continuing preservation of visual acuity for patients re-randomized to continue pegaptanib. Patients who were re-randomized to discontinue pegaptanib after one year, lost visual acuity during the second year.

Summary of Mean Changes in Visual Acuity from Baseline to Weeks 6, 12, 54 and 102 (LOCF)

	EOP 1003			**EOP 1004**		
	0.3-0.3	**0.3-discontinued**	**Sham-sham/sham+discontinued**	**0.3-0.3**	**0.3-discontinued**	**Sham-sham/sham+discontinued**
N	67	66	54	66	66	53
Mean change in VA Week 6	-1.9	-0.0	-4.4	-1.9	-2.0	-3.4
Mean change in VA Week 12	-4.3	-2.0	-4.8	-2.8	-2.2	-4.7
Mean change in VA Week 54	-9.6	-4.3	-11.7	-8.0	-7.6	-15.6
Mean change in VA Week 102	-10.8	-9.7	-13.1	-8.0	-12.7	-21.1

Data over a two-year period indicate that Macugen treatment should be initiated as early as possible. In advanced disease the initiation and continuation of Macugen therapy should consider the potential for useful vision in the eye.

Macugen therapy administered to both eyes concurrently has not been studied.

The safety and efficacy of Macugen beyond two years has not been demonstrated.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Macugen in all subsets of the paediatric population in age-related macular degeneration. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption:
In animals, pegaptanib is slowly absorbed into the systemic circulation from the eye after intravitreal administration. The rate of absorption from the eye is the rate-limiting step in the disposition of pegaptanib in animals and is likely to be in humans. In humans, the average ± standard deviation apparent plasma half-life of pegaptanib after a 3 mg (10-times the recommended dose) monocular dose is 10 ± 4 days.

A mean maximum plasma concentration of about 80 ng/ml occurs within 1 to 4 days after a 3 mg monocular dose in humans. The mean area under the plasma concentration-time curve (AUC) is about 25 μg·hr/ml at this dose. Pegaptanib does not accumulate in the plasma when administered intravitreally every 6 weeks. At doses below 0.5 mg/eye, pegaptanib plasma concentrations do not likely exceed 10 ng/ml.

The absolute bioavailability of pegaptanib after intravitreal administration has not been assessed in humans, but is approximately 70-100% in rabbits, dogs and monkeys.

In animals that received doses of pegaptanib up to 0.5 mg/eye to both eyes, plasma concentrations were 0.03% to 0.15% of those in the vitreous humour.

Distribution, biotransformation and elimination:
In mice, rats, rabbits, dogs and monkeys, pegaptanib distributes primarily into plasma volume and is not extensively distributed to peripheral tissues after intravenous administration. Twenty-four hours after intravitreous administration of a radiolabeled dose of pegaptanib to both eyes of rabbits, radioactivity was mainly distributed in vitreous humour, retina and aqueous humour. After intravitreal and intravenous administrations of radiolabeled pegaptanib to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreal dose) were obtained in the kidney. In rabbits, the component nucleotide, 2'-fluorouridine is found in plasma and urine after single radiolabeled pegaptanib intravenous and intravitreal doses. Pegaptanib is metabolised by endo- and exonucleases. In rabbits, pegaptanib is eliminated as parent drug and metabolites primarily in the urine.

Special populations:
Pegaptanib pharmacokinetics is similar in female and male patients and within the age range 50 to 90 years.

Pegaptanib sodium has not been adequately studied in patients with creatinine clearance below 20 ml/min. A decrease in creatinine clearance down to 20 ml/min may be associated with up to a 2.3-fold increase in pegaptanib AUC. No special considerations are needed in patients with creatinine clearance above 20 ml/min who are treated with the recommended dose of pegaptanib sodium 0.3 mg.

Pegaptanib pharmacokinetics have not been studied in patients with hepatic impairment. The systemic exposure is expected to be within a well tolerated range in patients with hepatic impairment, as a 10 fold higher dose (3 mg/eye) was well tolerated.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. There are no studies on the carcinogenic potential of pegaptanib.

Pegaptanib produced no maternal toxicity and no evidence of teratogenicity or foetal mortality in mice at intravenous doses of 1 to 40 mg/kg/day. Reduced body weight (5%) and minimal delayed ossification in forepaw phalanges were observed, only at exposure levels based on AUC of over 300 fold greater than that expected in humans. These finding are therefore considered to be of limited clinical relevance. In the 40 mg/kg/day group, pegaptanib concentrations in the amniotic fluid were 0.05% of the maternal plasma levels. There are no reproductive toxicity studies in rabbits.
No data are available to evaluate male or female mating or fertility indices.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Monobasic sodium phosphate monohydrate
Dibasic sodium phosphate heptahydrate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2ºC to 8ºC). Do not freeze.
The solution to be injected should reach room temperature (below 25°C) before injecting.

This medicinal product should be discarded if kept at room temperature for more than two weeks. To prevent contamination, the syringe should not be removed from the pouch until the patient has been prepared for injection.

6.5 Nature and contents of container

Each pack contains a pouch in a carton containing a 1 ml pre-filled syringe, Type 1 glass, sealed with an elastomeric (brombutyl rubber) plunger stopper and a pre-attached plunger rod, held by a plastic clip. The syringe has a pre-attached polycarbonate plastic luer lock adaptor and the tip is sealed with an elastomeric (bromobutyl/synthetic isoprene) tip cap.

Each pre-filled syringe contains approximately 0.25-0.27 ml of solution.
Each carton contains one pre-filled syringe in a pouch (single dose pack).
The pack is supplied without a needle.

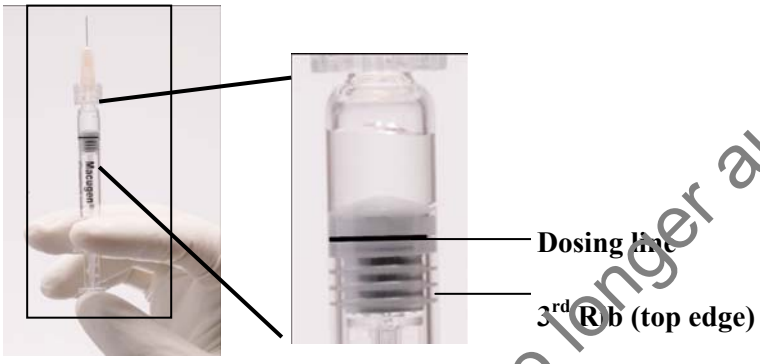
6.6 Special precautions for disposal and other handling

Macugen is for single use only. If the solution appears cloudy, particles are observed or if there is evidence of damage to the syringe, or if the plastic clip is missing or not attached to the syringe, that Macugen dose should not be used.

Prior to the administration, the syringe should be removed from the plastic clip and the tip cap removed. A 27 or 30 G x ½ inch needle should be attached to the luer lock adaptor, to allow the administration of the medicinal product (see Figure 1, below).

<u>CAUTION:</u> Since the pre-filled syringe contains more medicinal product volume (250-270 microlitres) than the recommended dose (90 microlitres), a part of the volume contained in the syringe has to be discarded prior to the administration. Follow the instructions below to expel the excess volume before injection.

Figure 1. <u>Before</u> expelling air bubble and excess drug

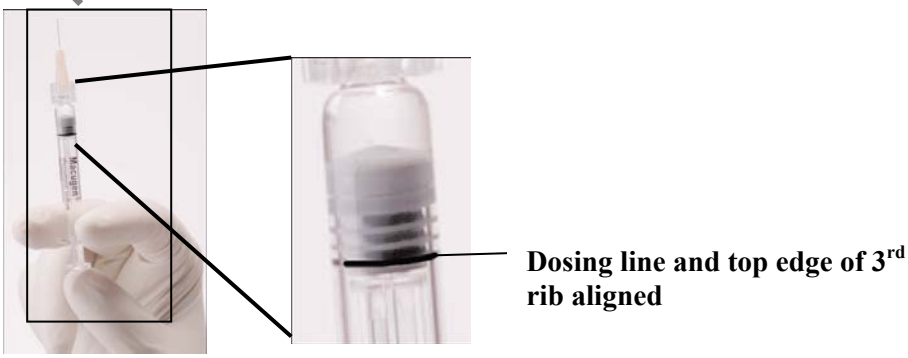


(Actual air bubble formation may vary)

The syringe should be checked with the needle pointing up for the presence of bubbles. If there are bubbles, the syringe should be gently tapped with a finger until the bubbles rise to the top of the syringe.

SLOWLY depress the plunger to eliminate all the bubbles and to expel the excess drug so that the **top edge of the 3rd rib on the plunger stopper aligns with the pre-printed black dosing line (See Fig 2, below). The plunger stopper should not be pulled back.**

Figure 2. <u>After</u> expelling air bubble and excess drug



At this point, the remaining content of the syringe should be injected.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

PharmaSwiss Česká republika s.r.o.
Jankovcova 1569/2c
170 00 Praha 7
Czech Republic

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/325/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31/01/2006
Date of latest renewal: 19/11/2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Belgium NV,
Rijksweg 12
B-2870 Puurs
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Macugen is marketed, at launch and after launch all ophthalmological clinics where Macugen is expected to be used are provided with an updated physician information pack containing the following elements:

- The Summary of Product Characteristics
- Physician safety brochure
- Intravitreal injection procedure video

- Intravitreal injection procedure pictogram
- Patient information

The physician safety brochure should contain the following key elements:

a) The intravitreal procedure as it was performed in the pivotal clinical studies, along with any technical improvements
b) Use of povidone iodine
c) Performing lid scrubs
d) Use of anaesthetic to ensure patient comfort
e) Sterile techniques to minimize the risk of infection
f) Use of antibiotics
g) Techniques for the intravitreal injection
h) Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, increased intraocular pressure, retinal injury, intraocular haemorrhage, traumatic cataract, hypersensitivity and injection of excess volume
i) Management of intraocular pressure
j) Management of endophthalmitis
k) Understanding the risk factors involved in developing endophthalmitis
l) Reporting of serious adverse events(reminder aid)

The patient information should contain the following key elements:

m) Key signs and symptoms of serious adverse events associated with the intravitreal injection procedure including endophthalmitis, increased intraocular pressure, retinal injury, intraocular haemorrhage, traumatic cataract, hypersensitivity and injection of excess volume
n) When to seek urgent attention from the health care provider

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Macugen 0.3 mg solution for injection
pegaptanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe provides a usable amount to deliver a single dose of 90 microlitres containing pegaptanib sodium, corresponding to 0.3 mg of the free acid form of the oligonucleotide.

3. LIST OF EXCIPIENTS

Sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, sodium hydroxide and hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
Delivers a single dose of 0.3 mg in 90 microliters
Pack of one pre-filled syringe, a plunger stopper and a pre-attached plunger rod. Needle is not provided.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravitreal use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CAUTION: Expel excess volume before injecting.
Align the third rib of the plunger stopper with the pre-printed black dosing line.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PharmaSwiss Česká republika s.r.o.
Jankovcova 1569/2c
170 00 Praha 7
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/325/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Macugen 0.3 mg injection
pegaptanib

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose: 0.3 mg/90 µl

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POUCH containing pre-filled syringe, a plunger stopper and a pre-attached plunger rod

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINSTRATION

Macugen 0.3 mg solution for injection
pegaptanib
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose: 0.3 mg/90 µl

6. OTHER

The pouch must not be opened until the patient has been prepared for injection.

CAUTION: Expel excess volume before injecting
Align the third rib of the plunger stopper with the pre-printed black dosing line.

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

Macugen 0.3 mg solution for injection
Pegaptanib

Read all of this leaflet carefully before you start your treatment with this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Macugen is and what it is used for

Macugen is a solution which is injected into the eye. Pegaptanib, the active substance of this medicine, inhibits the activity of the factor involved in the abnormal formation of new blood vessels in the eye, known as Vascular Endothelial Growth Factor$_{165}$ (VEGF$_{165}$).

Macugen is used for the treatment of the wet form of age-related macular degeneration (AMD). This disease leads to vision loss resulting from damage to the central part of the retina (called the macula), at the back of the eye. The macula enables the eye to provide the fine central vision that is needed for activities such as driving a car, reading fine print and other similar tasks.

In the wet form of AMD, abnormal blood vessels grow under the retina and macula. These new blood vessels may bleed and leak fluid, causing the macula to bulge or lift up, thus distorting or destroying central vision. Under these circumstances vision loss may be rapid and severe. Macugen works by inhibiting the growth of these abnormal blood vessels and by stemming the bleeding and leakage. The medicine is used for the treatment of all types of abnormal blood vessels growth in adult AMD patients.

2. What you need to know before you are given Macugen

You must not be given Macugen:
If you are allergic to pegaptanib or any of the other ingredients of this medicine (listed in section 6).
If you have an active or suspected infection in or around the eye.

Warnings and precautions
Talk to your doctor before you are given Macugen.

Occasionally, an infection or bleeding in the eye can occur after Macugen injection (in the next two weeks). It is important to identify and treat these types of conditions as soon as possible. Please tell your doctor immediately if you notice any of the following symptoms: eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, increased number of small particles in your vision. If your doctor cannot be reached for any reason, an alternate doctor should be contacted immediately.

In some patients the pressure inside the treated eye may increase for a short period directly after the injection. Your doctor may monitor this after each injection.

Soon after the injection serious allergic reactions may occur. The symptoms you might experience and the instruction what to do in such cases are described in section 4 of this leaflet.

Children and adolescents
Macugen should not be used in children and adolescents under 18 years old.

Other medicines and Macugen
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before Macugen treatment.

- There is no experience of using Macugen in pregnant women. Macugen should not be used during pregnancy unless the potential benefit outweighs the potential risk to the unborn child. If you are pregnant discuss this with your doctor before treatment with Macugen.
- Macugen is not recommended during breastfeeding as it is not known whether Macugen passes into human milk. Ask your doctor or pharmacist for advice before starting Macugen treatment.

Driving and using machines
You may experience temporary visual blurring after receiving Macugen. If you are affected, do not drive or use machines until this resolves.

Important information about some of the ingredients of Macugen
This medicine contains less than 1 mmol sodium (23 mg) per 90 microlitre dose, i.e. essentially 'sodium-free' (see section 6).

3. How you will be given Macugen

All injections of Macugen will be administered by your doctor.

Macugen is administered as a single injection (0.3 mg) into your eye at intervals of 6 weeks (i.e. 9 times per year). The injection is given into the vitreous of the eye, which is the jelly-like substance inside the eye. Your doctor will monitor your condition and recommend how long you should be treated with Macugen.

Before the treatment is given your doctor may ask you to use antibiotic eye drops, or to wash your eyes carefully. Your doctor will also give you some local anaesthetic (numbing medicine). This will reduce or prevent any pain you might have with the injection.
Please do not forget to tell your doctor if you are known to be allergic to any substance.

After each injection you might be asked to use antibiotic eye drops (or another type of antibiotic treatment) to guard against eye infection.

If you have been given more Macugen than you should have
In the case excess Macugen volume is injected, serious increase in intraocular pressure may occur. Whenever you'll experience vision disturbances, eye discomfort/pain, eye redness or nausea and vomiting, immediately refer to your doctor and tell about your symptoms.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Cases of serious allergic reaction, including anaphylactic reaction and angioedema of which symptoms are described below, has been reported soon after the injection. Please seek immediate medical help if you experience any of the following soon after the injection: sudden onset of breathing difficulty or wheezing, swollen mouth, face, hands or feet, itching skin, fainting, rapid pulse, stomach cramps, nausea, vomiting or diarrhoea. Frequency of these side effects cannot be estimated from the data available.

Uncommonly, an infection in the internal portion of the eye can occur after two weeks following Macugen treatment. The symptoms you might experience are described in section 2 of this leaflet ("Warnings and precautions"). Please read section 2. It tells you what to do if you have any of these symptoms.

Other possible side effects are as follows:

Very common (may affect more than 1 in 10 people)

These side effects are most probably caused by the injection procedure rather than the medicine, and include:

- eye inflammation
- eye pain
- increased pressure inside the eye
- small marks on the eye surface (punctate keratitis)
- small particles or spots in your vision (vitreous floaters or opacities).

Common (may affect up to 1 in 10 people)

Other common eye side effects reported to be possibly caused by the medicine or by the injection procedure include:

- blurred vision
- visual disturbance
- eye discomfort
- decreased vision
- increased sensitivity to light, appearance of flashing lights
- bleeding that occurs around the eye (periorbital bleeding)
- bloodshot eye (conjunctival haemorrhage)
- disorder of the jelly portion inside the eye (vitreous disorder), such as displacement or tear (vitreous detachment)
- clouding of the lens (cataract)
- disorder of the surface of the eye (cornea)
- swelling or inflammation of the eyelid, swelling of the area on the inside of the eyelid or the outer surface of the eye (conjunctiva)
- eye inflammation, tears, inflammation of the conjunctiva (conjunctivitis), dryness, eye discharge, eye irritation, itching of the eye, eye redness or enlargement of the pupil

Other common non-visual side effects reported to be possibly caused by the medicine or by the injection procedure include:

- headache
- nasal discharge.

Uncommon (may affect up to 1 in 100 people)

Uncommon eye side effects reported to be possibly caused by the medicine or by the injection procedure include:

- inflammation of your eye or of the outer surface of the eye

- bleeding in the eye or the internal portion of the eye (vitreous)
- eye strain
- inflammation of the central part of the surface of the eye (keratitis)
- small deposits on the eye or on the surface of the eye (cornea), deposits in the back of the eye,
- itching of the eyelids
- disturbance in your eye's reaction to the light (pupillary reflex impaired)
- small erosion on the central part of the surface of the eye (cornea)
- drooping eyelid
- scar inside the eye (retinal scar)
- small lump on your eyelid due to inflammation (chalazion)
- decreased pressure inside the eye
- injection site reaction, injection site vesicles
- displacement or tear of a layer in the back of the eye (retina)
- disorder of the pupil, of the coloured part of the eye (iris)
- retinal artery occlusion
- eversion of the eyelid, eye movement disorder, eyelid irritation
- blood in your eye, discoloured eye, deposit eye
- inflammation of the eye (iritis)
- optic nerve cupping
- deformation of the pupil
- occlusion of the vein at the back of the eye
- discharge of inner jelly of the eye

Uncommon non-visual side effects reported to be possibly caused by the medicine or by the injection procedure include:

- nightmare, depression, deafness, vertigo
- palpitations, high blood pressure, dilatation of the aorta (the main blood vessel)
- inflammation of the higher respiratory tract, vomiting, indigestion
- irritation and inflammation of the skin, hair colour changes, rash, itching,
- night sweats, back pain, tiredness, shivering, tenderness, chest pain, sudden fever and flu-like symptoms (generalised aches and pains)
- elevation of the liver enzymes, abrasion.

There is a small risk of a slight lasting increased pressure inside the eye after repeated injection in the eye.

Reporting of side effects
If you get any side effects, talk to your doctor , pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Macugen

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2ºC - 8ºC).
Do not freeze.

The medicine must be discarded if kept at room temperature for more than two weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Macugen contains

- The active substance is pegaptanib. Each single dose pre-filled syringe delivers a dose of 0.3 mg pegaptanib in 90 microlitres.

- The other ingredients are sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, sodium hydroxide and hydrochloric acid (for pH adjustment) and water for injections. For additional information regarding sodium content of Macugen, see section 2.

What Macugen looks like and contents of the pack

Macugen solution for injection is supplied in a single dose pack.

Each pack contains a pouch in a carton, containing a pre-filled syringe Type I glass, filled with 0.25-0.27 ml of solution, sealed with an elastomeric plunger stopper and a pre-attached plunger rod, held by a plastic clip. The syringe has a pre-attached polycarbonate plastic luer lock adaptor and the tip is sealed with an elastomeric tip cap.
The pack is supplied without a needle.

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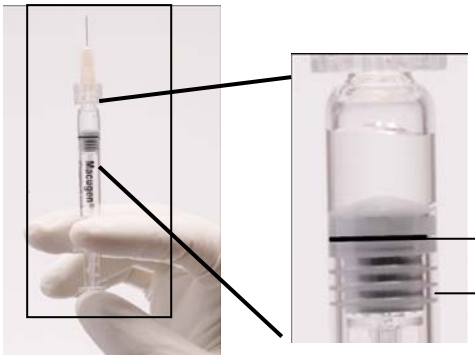
This leaflet was last revised in
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

The following information is intended for healthcare professionals only:

<u>CAUTION:</u> Since pre-filled syringe contains more medicinal product volume (250-270 microlitres) than the recommended dose (90 microlitres), a part of the volume contained in the syringe has to be discarded prior to the administration. Follow the instruction below to expel the excess volume before injection.

Figure 1. <u>Before</u> expelling air bubble and excess drug



(Actual air bubble formation may vary)

The syringe should be checked with the needle pointing up for the presence of bubbles. If there are bubbles, the syringe should be gently tapped with a finger until the bubbles rise to the top of the syringe.

SLOWLY depress the plunger to eliminate all the bubbles and to expel the excess drug so that the **top edge of the 3rd rib on the plunger stopper aligns with the pre-printed black dosing line (See Figure 2, below). The plunger stopper should not be pulled back.**

Figure 2. <u>After</u> expelling air bubble and excess drug

At this point, the remaining content of the syringe should be injected.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.