1. Introduction

Age-related macular degeneration

Age-related macular degeneration (AMD) is a disease characterized by progressive degenerative abnormalities in the macula, a small area in the central portion of the retina with the highest visual acuity.

AMD is the major cause of vision loss in the elderly population in the Western world. Although the disease rarely results in complete blindness and peripheral vision may remain unaffected, central vision is gradually blurred, severely affecting ordinary daily activities.

AMD is characteristically a disease occurring in older patients. Population-based epidemiologic studies have provided estimates of prevalence and incidence of AMD among various racial/ethnic groups around the world and have shown that AMD is rare before 55 years of age, that it is more common in persons 75 years of age or older, and that it is less common in blacks than whites.

AMD is classified as two different types: the non-exudative (or dry) form and the exudative (or wet) form of the disease. The dry from is the most prevalent, accounting for 90% of cases of the disease. It is not uncommon that the dry form develops into the wet, neo-vascular form of AMD. Exudative AMD, the neovascular form of the disease, is responsible for the majority of cases of severe vision loss. Exudative AMD is characterized by the formation of a choroidal neovascular network beneath the retina (CNV). This neovascular membrane leaks blood and fluid under the retina and eventually progresses to scar formation with destruction of the macula and loss of vision. The prevalence of exudative AMD in developed countries rises exponentially with age, with near absence at age 50 to 1% at age 70 and 5% at age 80.

The pathogenesis of CNV formation is poorly understood and involves, among many factors, vascular growth factors (including but not limited to VEGF), proteases (serine- and metallo-proteases and their inhibitors) and inflammation (inflammatory cells, bone marrow-derived progenitors, chemokines).

There is no curative treatment for AMD. Treatment available includes low vision rehabilitation. A certain percentage of patients with exudative AMD can benefit from laser treatment with traditional photocoagulation laser or photodynamic therapy (PDT). Photodynamic therapy with verteporfin (Visudyne™) has been approved for the treatment of predominantly classic or occult subfoveal exudative (neovascular) AMD on the basis of decreased visual deterioration in treated patients compared to controls. AMD is currently an area with a need for more efficacious treatments and for treatments applicable to all forms of neovascular AMD.

Pegaptanib

Pegaptanib belongs to the pharmacotherapeutic group of "other ophthalmologicals", ATC code: 01XA17. 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. $VEGF_{165}$ 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.

To increase the intravitreal residence time, a 40 kD branched polyethylene glycol (PEG) molecule has been conjugated to the oligonucleotide. Pegaptanib has the following sequence of nucleotides and functional groups:

5’-[40kD]-[HN-$(CH_2)_5$O]-pC_fpG_mpG_mpA_rpA_rpU_fpC_fpA_mpG_mpU_fpG_mpA_mpA_m pU_fpG_mpC_fpU_fpU_fpA_mpU_fpA_mpC_fpA_mpU_fpC_fpC_fpG_m3’-p-dT

Secondary structure:

where

- [40kD] represents the two 20 kD PEG chains.
- [HN-$(CH_2)_5$O] represents the amino linker connecting PEG and the oligonucleotide via a phosphodiester bond.
- p represents the negatively charged phosphodiester functional groups that have Na^+ counter ions.
- G_m or A_m and C_f or U_f and A_r represent 2-methoxy, 2-fluoro and 2-hydroxy variants of their respective purines and pyrimidines.
- C, A, U and G code for cytidylic, adenylic, uridylic and guanylic acids.

A clinical development program to investigate the use of pegaptanib sodium in the treatment of exudative AMD began in 1999. The nonclinical program began in 1996 and spans the duration of clinical development. The development program has been conducted entirely in male and female over 50-yr patients with exudative AMD (N= 1210) instead of normal volunteers as the product is delivered by an intravitreous injection. The risks of such injections were felt to be inappropriate for healthy volunteers.

GMP inspections were performed at the site of manufacture of the active substance and of the finished product manufacturing site. Both sites were found to operate in compliance with EU GMP.

2. Part II: Chemical, pharmaceutical and biological aspects

Introduction

Pegaptanib is a synthetic oligonucleotide. Pharmaceutically, the product is presented as a sterilised injection 3.47 mg/ml (based on the oligonucleotide weight). The proposed posology is 0.3 mg, every six weeks by means of an intravitreal injection (IVT) into the eye using a single-dose, pre-filled syringe. Each syringe contains a nominal delivered volume of 90 µl. The drug product is presented in a 1 ml glass barrel syringe sealed with a rubber plunger stopper. The syringe has a fixed needle with a rubber needle shield and a rigid plastic outer shield. A plastic syringe plunger and flange adapter are also supplied for administration purposes.

Evidence has suggested a causal role of vascular endothelial growth factor (VEGF) in several diseases of the human eye in which neovascularization and increased vascular permeability occur. Pegaptanib has been developed to bind and block the activity of extracellular VEGF, specifically the 165-amino-acid isoform ($VEGF_{165}$).

Active Substance

The active substance is present as the sodium salt, Pegaptanib Sodium, and is a 28-mer oligonucleotide aptamer (L. *aptus,* to fit; Gk. *meros,* part or region) covalently linked to two 20-kD polyethylene glycol (PEG) chains. Two of the nucleotides are ribonucleotides, one is a deoxy ribonucleotide, while the rest of the nucleotides contain modified sugars. The modified sugars confer increased resistance towards nuclease degradation of the oligonucleotide. The different nucleotides are linked via 5’- to 3’-phosphodiester linkages to yield the 28-mer oligonucleotide. The 3’-end thymidine contains a 3’-3-linkage to the penultimate 2’methoxyguanosine. The 5’-end of the oligonucleotide contains a lysine residue (pentylaminolinker), whose amino groups serve to attach the two PEG units.

Pegaptanib sodium is hydrophilic and very soluble in water and soluble in a number of organic solvents.

- Manufacture

The manufacture of pegaptanib sodium includes the following steps

- Oligonucleotide Synthesis, Purification of nonPEGylated Oligonucleotide, PEGylation Reaction, PEGylated Oligonucleotide Purification and drying.

The oligonucleotide is manufactured by solid phase organic synthesis using well-established methodology.

- Characterisation

The drug substance is an aptamer, meaning it is the secondary structure (i.e. folding) of the oligonucleotide chain that governs the structure which is required for its effect on binding to $VEGF_{165}$. The folding is in turn governed by the primary structure (i.e. nucleotide sequence); hence structural characterisation of drug substance involves determination of primary as well as secondary structure.

The methodologies applied for structural characterisation are well covered. The molecular sequence for the pegaptanib sodium molecule was established through a combination of spectroscopic, physicochemical and biological techniques. The impurities present in oligonucleotides have been investigated.

- Specification

A variety of tests have confirmed the qualitative and quantitative characteristics of the active substance by means of a combination of relevant physicochemical and biological methods.

Batch analyses indicate satisfactory compliance with the agreed specification and uniformity from batch to batch.

- Stability

The active substance is stored in sealed glass vials. Validated stability-indicating methods have been developed and stress studies have demonstrated that it is prone to degradation from light, oxidation and heat (40°C/75%RH). Formal studies according to ICH guidelines have been performed at –20 °C (± 5 °C), recommended storage conditions, and 5 °C (± 3 °C), accelerated storage conditions, for three batches. Supportive data for three batches stored at recommended and accelerated storage conditions, up to 24 months is also presented. The results confirm the retest period and storage conditions of the active substance.

Medicinal Product

- Pharmaceutical Development

Aptamers bind with high specificity and affinity to target molecules, including proteins, and as expected, the binding relies on the specific three-dimensional conformation of the properly folded aptamer. In order to prolong activity at the site of action, the sugar backbone of pegaptanib was modified to prevent degradation by endogenous endonucleases and exonucleases, and the polyethylene glycol moieties were added to increase the half-life of the drug in the vitreous humour.

A sterile aqueous parenteral solution was developed as a rational presentation for this product.

Compatability studies have demonstrate that monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, sodium chloride, hydrochloric acid and sodium hydroxide, at the concentrations used in the formulation, are all compatible with pegaptanib sodium in solution.

Due to the instability of the active substance to terminal sterilisation , an aseptic, filter sterilisation process has been developed.

- Manufacture of the Product

Macugen is manufactured by dissolving pegaptanib sodium into a physiologically-compatible solution. This is followed by pH adjustment, assay, and dilution to the desired strength. The solution is sterilized by filtration and filled into syringes under aseptic conditions. The syringes are labelled and then packaged into a foil pouch. The process uses conventional equipment and facilities. There are no unduly critical steps and the validation of this standard process is satisfactory.

- Product Specification

The specification of the product is based on that of the active substance with additional pharmaceutical tests. Fully characterised reference standards are used in the tests. In addition the specification also includes tests for delivered volume, osmolality, pH, sterility, endotoxin, and particulate contamination..

Batch analyses indicate satisfactory compliance with the agreed specification and uniformity from batch to batch.

- Stability of the Product

Stability results have been provided for three primary stability lots at the 0.3 mg strength the product in the configuration as intended for market. In addition three supportive stability lots at the 1 mg strength are presented in the proposed commercial packaging (syringe in foil pouch).

Tests were performed at 2 – 8°C long term, and 25 °C accelerated, under ICH conditions and the characteristics were monitored using stability-indicating methods.

Results support the shelf-life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

This synthetic peptide has been manufactured characterised and controlled in a way that indicates satisfactory purity and uniformity, and the medicinal product has been developed utilising molecular development aspects in addition to standard pharmaceutical ones in order to achieve the desired clinical effect.

The finished product is manufactured and tested in a way that indicates a reliable and reproducible product in the clinic, throughout the shelflife.

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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
At the time of the CHMP opinion, a number of minor quality issues related chiefly to method development and validation and ongoing stability studies were unresolved; the applicant agreed to resolve these as FollowUp Measures within an agreed timeframe.

3. Part III: Toxico-pharmacological aspects

Introduction

The non-clinical pharmacokinetics and toxicity of pegaptanib was evaluated after of both IVT and intravenous (IV) administration with the main studies performed in rats, rabbits and dogs. A limited reproductive toxicology program was conducted. While no carcinogenicity studies were performed, pegaptanib and its potential metabolites, the component's nucleosides, were evaluated with respect to genotoxicity. Most pivotal non-clinical studies were done according to GLP.

Pharmacology

Inhibition of VEGF has been shown to, at least partially, prevent neovascularisation in several models, both in models using pegaptanib, as those submitted with this application, but also in published studies utilising antibodies and small molecules.

The aptamer of pegaptanib was isolated from RNA libraries containing random nucleotides and further modified to obtain high selectivity and affinity (picomolar region) towards especially $VEGF_{165}$. Addition of the PEG-moiety reduced the affinity ~4-fold.

The pharmacology studies were undertaken to demonstrate the following attributes of pegaptanib sodium:

- High affinity and selectivity for the $VEGF_{165}$ isoform over $VEGF_{121}$ isoform.

- *In vitro* functional studies to confirm that pegaptanib's high affinity for this isoform translates to

$VEGF_{165}$ antagonism.

- *In vivo* studies to demonstrate functional antagonism of VEGF- mediated changes in angiogenesis and vascular permeability.

- Primary pharmacodynamics (*in vitro/in vivo*)

The pharmacological characterisation of pegaptanib included *in vitro* studies on pegaptanib binding to $VEGF_{165}$ and related ligands, inhibition of VEGF-binding to its receptors, inhibition of functional effects following $VEGF_{165}$ binding to its receptors (cellular proliferation, calcium flux, and tissue factor gene expression), and *in vivo* effects on vascular permeability and angiogenesis.

– *In vitro* studies

The series of *in vitro* studies that characterized pegaptanib antiangiogenic and anti-permeability pharmacology included studies on binding affinity and selectivity of pegaptanib to $VEGF_{165}$ relative to other VEGF isoforms and associated proteins, pegaptanib $VEGF_{165}$ antagonist activity in human umbilical vascular endothelial cell (HUVEC) proliferation and tissue factor expression assays, pegaptanib inhibitory effects on VEGF binding to VEGF receptor Fc constructs, and pegaptanib inhibition of calcium mobilization in HUVECs.

Pegaptanib binds *in vitro* to purified recombinant $VEGF_{165}$ with high affinity but does not bind to the smaller isoform $VEGF_{121}$ or any of the VEGF-related proteins tested (VEGF-B, VEGF-C, and PlGF). Pegaptanib also binds to $VEGF_{188}$, the murine ortholog of human $VEGF_{189}$, which is normally bound to the cell surface. Binding to $VEGF_{188}$ was significant, albeit less than obtained with purified $VEGF_{165}$. Pegaptanib effectively inhibits $VEGF_{165}$ binding to its cellular receptors, as seen with both purified constructs of the Flt-1 (VEGFR-1), KDR (VEGFR-2), and NP-1 receptors and on the cell surface of cultured human endothelial cells. Pegaptanib sodium has a three-dimensional conformation that enables it to bind $VEGF_{165}$ much like an antibody.

In addition, $VEGF_{165}$-induced cellular proliferation, calcium mobilization, and tissue factor gene expression are effectively inhibited in cultured human umbilical vein endothelial cells (HUVECs) treated with pegaptanib sodium. No investigations have been carried out on choroidal endothelial cells. The binding of the aptamer portion of pegaptanib is strong, short-lived and reversible. There is no data to show that the sequence does not bind to any off-target ligands/receptors.

– *In vivo* studies

In vivo, administration of pegaptanib sodium inhibited hypoxia-induced retinal neovascularization in a murine model of retinopathy of prematurity, VEGF-induced corneal angiogenesis in a rat corneal pocket model, and dermal vascular leakage in a dermal vascular permeability (modified Miles) assay in guinea pigs. Pegaptanib has not been tested in an animal model for choroidal neovascularisation. In the hypoxia induced neovascularisation model (retinopathy of prematurity, ROP) in rodents, the key role of VEGF in abnormal vascular growth was confirmed. The Applicant has generated additional data showing that the intravitreal injections in the ROP model caused a high variability and poor recovery of intravitreal concentrations of pegaptanib. Therefore, the i.p. route of administration was chosen. In the new studies, ocular neovascularisation could be prevented and a 50% inhibition of retinal vascular growth was achieved at 0.21 nM (~1.95 ng/ml). Extrapolation of data indicates that levels above the IC_{50}-values are obtained clinically at a 6-week dosing interval if the human vitreous T½ exceeds 4 days. Even if the data obtained have their weaknesses, the submitted study is reasonable. Further, the Applicant plans a program to evaluate the applicability of ^{19}F-pegaptanib MRS to obtain repeated non-invasive measures of pegaptanib levels in the human eye.

- Secondary pharmacodynamics

Even though pegaptanib is highly selective for $VEGF_{165}$ compared to closely related targets, no data was presented to show that it does not bind to any off-target ligands/receptors, or whether the de-pegylated (intact or degraded) aptamer may have antisense properties.

- Safety pharmacology

Pegaptanib sodium was evaluated in animal models for cardiovascular, respiratory and neurobehavioral effects, at IV administered doses with associated systemic exposures up to 10-fold

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