STDG/SMC/MDM

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Agenzia Italiana del Farmaco

AIFA

Director General

Rome 12/03/14

Dr. Paola Testori Coggi
European Commission
Director-General in the Directorate-General
for Health and Consumers
1049 Brussels, Belgium

Ref: Avastin (Bevacizumab) or Lucentis (Ranibizumab) Intravitreal use

Madam Director General / Dear Dr. Testori Coggi

In December 2012 the Italian Technical Scientific Committee (CTS) of AIFA, followed the decision enacted on 30th August 2012 by the CHMP of EMA, which modified the risk/benefit profile of Avastin. The CHMP decision altered the point 4.4 of Avastin SpC as follows:

"Intravitreal use: Avastin is not formulated for intravitreal use.

Eye disorders

Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

Systemic effects following intravitreal use

A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and

arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors."

This information related to the medical product's safety has led to the exclusion of intravitreal Bevacizumab from the list of the Italian Law 648/96 which allowed the reimbursement by the National Health System of off-label medicines and only when in-label medicines are not present.

AIFA, taking in account the CTS opinion, in its role to protect public health, has communicated to ophthalmologists who eventually wanted to continue the off-label treatment with Avastin to carefully evaluate the risk/benefit balance for Avastin, and to inform the patients about the risk related to its intravitreal treatment. In addition, the Agency, in order to follow up patients treated with Avastin intravitreally, tried to gather information from all the Italian Regions. After 18 months only 34 ADRS were sent on a total of 44.071 patients treated, strongly suggesting that off-label ADRs are under-reported. About two weeks ago, as you are certainly aware, the Italian Antitrust Authority has found Roche and Novartis, the two MAHs of Avastin and Lucentis respectively, guilty of a cartel agreement and announced a fine for 182M Euro.

This decision has stirred a media hype, even brought false accusations of corruption to AIFA, and the Italian Parliament may consider the possibility of discussing a new law which would modify the off-label use.

AIFA would like to receive DG-SANCO opinion about the role of a National Competent Authority in such a situation (i.e. allowing off-label use in presence of such specific SpC expressed warnings).

Looking forward to your reply, I remain respectfully your,

(Luca Pani)