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SUMMARY

Anti-angiogenic Drugs in the Treatment for Age-related Macular Degeneration: Issues Associated with Their Use in Québec

Notice

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SUMMARY

Age-related macular degeneration (AMD) is a retinal disease that causes a loss of central vision potentially leading to blindness. The exudative or wet form of the disease is less common but more serious than the atrophic or dry form of the disease, and is responsible for 90% of major vision loss due to AMD.

Three treatment options slow the progression of exudative AMD: laser photocoagulation, photodynamic therapy and anti-angiogenic agents. These agents are antibodies that inhibit a key protein (vascular endothelial growth factor, VEGF) responsible for neovascularization (abnormal growth of blood vessels) in the retinas of subjects with AMD. The anti-VEGF agents used in monotherapy to inhibit neovascularization are pegaptanib (Macugen), ranibizumab (Lucentis) and bevacizumab (Avastin). It should be noted that Macugen is virtually no longer used in Québec.

Lucentis has been approved in Canada for the treatment of AMD, whereas Avastin, approved for the treatment of colorectal cancer and certain other cancers, is also used as an off-label treatment for AMD. Both drugs are produced by the same manufacturer, which has not shown any intention to apply for approval of Avastin to treat AMD. In Québec as elsewhere, the use of Avastin for the treatment of AMD began before Lucentis was approved, and, owing to its recognized clinical benefit, the use of Avastin has remained firmly rooted in practice even though its efficacy and safety for AMD had not been proven in clinical studies. However, such off-label use of medication can be found also in the treatment of other diseases.

Scientific evidence on the efficacy, safety and cost of anti-VEGF agents, especially ranibizumab (Lucentis) and bevacizumab (Avastin), is addressed in greater detail in the note preparatory to this document. This note, prepared by INESSS at the request of the Minister of Health and Social Services, followed the publication of the first major study comparing the two drugs (Comparison of Age-Related Macular Degeneration Treatments Trials, CATT). Moreover, concerns over the safety and preparation of Avastin when used in the form of an intravitreal injection had already been raised before the recent warning letters issued by the U.S. Food and Drug Administration regarding this particular issue.

Given that the Minister wanted all parties concerned in Québec to have access to information that would help them make informed decisions regarding the use of anti-angiogenic agents in the treatment of AMD, he also asked INESSS for an advisory opinion on this issue. INESSS therefore formed a committee of experts and representatives of its network partners to help shed light on the contextual aspects and issues related to this practice. The Minister's request indicated that this work should not adopt the perspective of entering these agents on the public medication lists.

Even if Avastin is used and covered by public insurance plans in a few Canadian provinces because of its low cost, the fact that it has not been approved for the treatment of AMD, combined with the limited evidence on its safe use, raises not only financial but also ethical, technical, logistical, legal and organizational issues, not to mention issues linked to drug accessibility and treatment quality. These numerous issues differ according to the main stakeholders concerned in Québec, that is, people with AMD, physicians, pharmacists, institutional administrators, regional administrators and ministry authorities.

In short, Lucentis has been approved by Health Canada for the treatment of AMD, while Avastin has not been approved. With regard to efficacy, evidence shows that Avastin is not inferior to Lucentis. However, Avastin's safety profile remains to be confirmed. The problem with safety arises from the fact that the commercial presentation of this drug is not adapted to intravitreal injections and includes handling not provided for in the product description.

For the purpose of minimizing the risks of product contamination and the potential adverse effects associated with them, the preparation and re-packaging of Avastin must be performed under strict sterile conditions, and a safe distribution mechanism must be planned to ensure the cold chain. Quality standards already govern the preparation of sterile products in pharmacies, and Québec's current experience shows that these requirements are being

met by community and health care institution pharmacists. As for Lucentis, its presentation allows for extemporaneous preparation and only the cold chain must be maintained until the time of intravitreal injection.

The preparatory note that we produced reported on the issues related to the accessibility of either of the drugs mentioned, whether related to their affordability or their availability, and indicated that further analysis of these issues was required. While Lucentis is covered as an exceptional medication by the Public Prescription Drug Insurance Plan (*régime public d'assurance médicaments*, RPAM) (and by most private insurers), Avastin, although used in current medical practice, may not be entered on the list of the RPAM because it is not an approved drug. Treatment with Avastin costs approximately 30 times less than treatment with Lucentis, but if it is administered in a hospital centre, it is not charged to treated people. In non-institutional facilities, the amount paid by patients for Lucentis depends on the rules set by their insurance plans; however, owing to an informal agreement between the Association des médecins ophtalmologistes du Québec (AMOQ) and the Ministère de la Santé et des Services sociaux (MSSS), treated people do not pay anything for Avastin received in a compounding pharmacy for professional use by a physician providing intravitreal injections.

In addition to the problems of affordability for treated people, the high cost of Lucentis leads to major budgetary consequences for institutions and for public and private insurance plans. Avastin is much less expensive, but its use could potentially be associated with a greater risk for major adverse effects, even though these remain relatively uncommon. Unless institutional boards of directors have adopted and signed official resolutions concerning the use of Avastin for the treatment of AMD, these adverse effects could oblige the institutions to pay compensation, where applicable. Be that as it may, decision makers are faced with difficult choices regarding the efficient use of current resources.

In this notice, INESSS also examined, for both drugs studied, the different issues related to the responsibilities all of the stakeholders concerned, along with the potential legal and ethical issues. These major issues arise mainly from the provisions of the Act Respecting Health Services and Social Services, the Medical Act, and the Pharmacy Act, as well as from their associated regulations and codes, especially the codes of ethics governing physicians and pharmacists. Special attention was paid to the right of treated people to receive scientifically appropriate services in personalized and safe manner, and to their right to be informed of the different treatment options, along with their generally associated risks and side effects, so that they may give their informed consent to any one of these types of treatments.

The analysis also reported on the major impact that will result from Health Canada's recent approval for the use of Lucentis for new indications, diabetic macular edema and retinal vein occlusion. These diseases, like AMD, are associated with aging, and it is highly likely that the manufacturer of this drug will submit an application to INESSS to enter the drug on the list of the RPAM. Furthermore, certain pharmaceutical companies are currently developing other anti-VEGF drugs, and some of these drugs are on the verge of being approved in other countries. In these circumstances, we can expect an increase in the intravitreal administration of anti-VEGF agents, such that the issues raised by their use will also become more prevalent. In the meantime, it would be important to keep a watch on the major studies underway, some of which will provide new scientific evidence on the adverse effects of Avastin. This notice should be reviewed when the scientific evidence from these studies becomes available.

Furthermore, on the basis of the identified issues and expert members' experience and knowledge of the field, the expert committee proposed a few other possible solutions to ensure its best use, combined with the efficient use of resources. These deserve careful examination, given the consequences they may have on practice both in the short term and in the years to come. Since these additional solutions were proposed by the members of this committee, they are presented in an addendum to this notice .

In conclusion, with the analysis presented in this advisory opinion, INESSS, in collaboration with the expert committee on the use of anti-VEGF agents for the treatment of AMD in Québec, hoped to shed as much light as possible on all the issues raised by their use. It is now up to all the parties concerned to make the necessary decisions regarding the use of either of these drugs that will be the most appropriate for health and well-being on both an individual and a collective level.