The European Alliance for Access to Safe Medicines (EAASM) - Public Comment Submission to the Essential Medicines List

24 February 2015

Ref: 20th Expert Committee application for inclusion of Ranibizumab (addition) in the WHO Essential Medicines List Section 21, Ophthalmological Preparations

Executive summary

The World Health Organisation (WHO) defines patient safety as “the prevention of errors and adverse effects to patients associated with health care.” Preventing harm to patients is challenging as risk will always be involved in the delivery of healthcare, but harm can be reduced by following regulations, guidelines and procedures already entrenched in most patient safety programmes. The World Health Organisation and selection of treatments on the Essential Medicines List (EML) are two key constituents to embedding patient safety in healthcare policies around the world.

The European Alliance for Access to Safe Medicines (EAASM - www.eaasm.eu) is a pan-European initiative dedicated to protecting patient safety by ensuring access to safe and legitimate medicines. The Alliance is formed by a cross-section of European patient safety stakeholders from a variety of backgrounds. Novartis and Bayer are members of EAASM, both companies have approved treatments of Neovascular age-related macular degeneration (nAMD). EAASM’s key activities include campaigning for the safer use of unlicensed or off-label medicines in Europe and internationally. In this instance, EAASM is eager to highlight the need to consider patient safety to particularly vulnerable patient groups who suffer from eye-diseases that disproportionately impacts people later in life and those suffering from diabetes.

A key pillar of EAASM’s advocacy is to ensure the use of approved treatments and technologies according to the medical need of the patient and that any prescribing for treatment beyond approved use, should be done only with the best medical interests of the patient in mind and with the patient’s fully informed consent.

EAASM believe the listing on the EML of licensed treatments is essential. A positive decision on the addition of Ranibizumab to EML is an opportunity to embed a precedent acknowledging the right of patients and prescribers to choose for the safety profiles of licensed products. Failure to do so will undermine patients’ rights and Good Medical practice (GMP) and General Medical Council (GMC) prescription guidelines.

EAASM believe it is essential that licensed treatments are available to patients so that they and their doctors can make fully informed decisions on the level of risk they wish to take. They are entitled to such a choice if they wish to reduce the inherent risks associated with their treatment. Our Alliance supports the listing of any licensed medicine on the EML; and do so in this instance for the treatment of nAMD; a disease that disproportionately impacts people later in life and those suffering from diabetes. For this reason, we support the addition of Ranibizumab on the EML for the treatment of nAMD and other eye diseases. Its addition to the list is very important from a patient safety angle and for prescribers to understand that they can choose licensed treatments. Currently, the EML does not encourage choice, since the only treatment for nAMD on the list is the off-label use of Bevacizumab.

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1 World Health Organisation. Genomic Resource Centre, Patient Safety
http://www.who.int/genomics/public/patientrights/en/
Failure to add a licensed product alongside an off-label product on the EML is by omission denying patients and prescribers the choice and obfuscating the option to treatment that uses a molecule specifically designed, tested, indicated and licensed for injecting in the eye. In the absence of any policing of the adherence to strict compounding guidelines, particularly vulnerable patient groups who suffer from eye-diseases are at further risk of infection which can have devastating results.

**About The European Alliance for Access to Safe Medicines (EAASM)**

The European Alliance for Access to Safe Medicines (EAASM) is a pan-European initiative dedicated to protecting patient safety by ensuring access to safe and legitimate medicines. *The Alliance has been formed by a cross-section of European patient safety stakeholders from a variety of backgrounds.* The European Alliance for Access to Safe Medicines (EAASM) was founded in 2007 with the clear objective of fighting against counterfeit medicines and promoting patient safety around Europe.

The EAASM is currently funded by a number of different companies. The EAASM accepts untied core funding from any legitimate source, other than when the core business or activity of the potential donor is opposed to the aims and objectives of the EAASM. Our funding partners include a number of major pharmaceutical companies. Of particular relevance to this expression of public support to the addition of Ranibizumab on the EML is the fact that both Novartis and Bayer are members. Both companies have approved treatments of Neovascular age-related macular degeneration (nAMD).

EAASM’s key activities include campaigning for the safer use of unlicensed or off-label medicines and also the exclusion of counterfeit and substandard medicines from the supply chain, raising public awareness around such issues, and campaigning for effective legislation and enforcement in relation to falsified medicines.

The EAASM Consensus Statement on the patient safety implications around the use of unlicensed and off-label medicines explains that there is an urgent need to address patient safety issues around the unlicensed/off-label use of medicines.

**Reasons for the Public Comments in support of the Novartis/Ranibizumab (addition) Application**

Medicines are rightly among the tightest regulated products in the world. They are licensed, for specific conditions, only after exhaustive trials. Manufactured to the highest standards and prescribed only after a consultation with a professional who has spent many years qualifying to practise, they are finally dispensed by another well-qualified professional, in strictly regulated conditions.

We support the listing of any licensed medicine on the EML. For this reason, we publicly support the addition of Ranibizumab on the EML for the treatment of nAMD and other eye diseases. Its addition to the list is crucial for patients and prescribers to understand that they can choose licensed treatments. Currently, the EML does not encourage choice, since the only treatment listed on the EML for nAMD is for the off-label use of Bevacizumab.

In this instance, we support the application submitted by Novartis for Ranibizumab to be added to the EML. Currently the only treatment listed on the EML for nAMD is for the off-label use of Bevacizumab; a positive decision on the only licensed application submitted to date for the treatment of nAMD would redress this situation.

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2 EAASM Consensus Statement on Unlicensed / Off-Label Medicines
3 When Is a Medicine Not a Medicine? (2011)
http://www.eaasm.eu/cache/downloads/cyhh53ous5k4k08csowocsw8/When_is_a_Medicine_Not_a_Medicine_Brochure%20FINAL.pdf
We highlight the following statements included in the Novartis / Ranibizumab application:

- Ranibizumab is a licensed medicine for the treatment of nAMD and as outlined in the Novartis application:
  - Ranibizumab is licensed and available in more than 100 countries for the treatment of nAMD, visual impairment due to DME and for visual impairment due to macular oedema secondary to BRVO and CRVO.
  - Ranibizumab is also licensed in more than 80 countries for the treatment of patients with visual impairment due to myopic CNV.
  - Ranibizumab is the standard-of-care first-line therapy in nAMD, DME, BRVO, CRVO and mCNV. Therefore, it has a proven track record for safety and efficacy in this indication and undergoes continuous safety monitoring.

As a licensed medicine packaged in the correct dosage form, Ranibizumab does not present the same infection risks associated with compounding issues prevalent in off-label use of Bevacizumab, which is currently the only option on the EML. Due to the lack of a specific mandatory mechanism for the reporting of adverse events associated with the use of off-label use of Bevacizumab for the treatment of nAMD, we can only rely on anecdotal evidence of instances where patients’ health or lives have been put at risk. 

An example to highlight the risk of using off-label/unlicensed medicine occurred in France, where a medicine for treating obesity in diabetic patients was, until it was finally banned, routinely prescribed for general weight loss in non-diabetic patients. The French authorities estimate between 500 and 2,000 resultant deaths.Æ

EAASM believes there is a public health imperative to monitor the safety of medicines which regrettably is not systematic in the case of off-label use of medicines. Tragically, people have died as adverse event reporting systems can fail to pick up critical side effects. This is because prescribing medicines not for the original licensed indication, in practice, may for a number of reasons, fall out of the adverse event reporting system and may therefore not be recorded properly. The consequence of this is that proper analysis and action may not be deemed necessary or legally binding by those involved. Today, there is no formalised procedure in place for reporting adverse events when using medicines off-label. For example, in the EU when a medicine is registered it must be subjected to Periodic Safety Update Reports (PSURs), covering all indications and including a risk: benefit analysis of the product in question. Additionally, Risk-management Plans (RMPs) have been required for all new products registered in the EU after July 2012. They are similar to PSURs in that they cover all available safety data relating to a product but instead of being an update, reflect the current state of knowledge about the risks inherent in using a particular product. However, there is no requirement to review off-label use reports that are not associated with an adverse reaction.

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5 FDA Recall notice: Clinical Specialties Issues Voluntary Nationwide Recall of Avastin Unit Dose Syringes due to Potential Serious Eye Infection (March 2013) [http://www.fda.gov/Safety/Recalls/ucm344377.htm](http://www.fda.gov/Safety/Recalls/ucm344377.htm)
8 EAASM Backgrounder: When is a medicine not a medicine? [http://www.eaasm.eu/cache/downloads/aWyvo0qvt40g0Wkgo8Cckws4/1428%20Off-label%20Backgrounder_04.pdf](http://www.eaasm.eu/cache/downloads/aWyvo0qvt40g0Wkgo8Cckws4/1428%20Off-label%20Backgrounder_04.pdf)
Patients wherever they live in the world have the right to be fully informed and consent to treatment. Informed consent includes providing all information about treatment, the risks and benefits, as well as alternative treatment options in written as well as verbal communication form. Without having a licensed medicine listed on the EML, such an option to choose a licensed product is not possible. The lack of transparency towards the patient is a concern to our Alliance. Patients with visual impairment are all the more vulnerable and less able to read product labelling and all the more reliant on their physician.

The medicine approval process is a complex one, requiring various laboratory and animal tests to discover how the drug works and whether it's likely to be safe and work well in humans. Licensed medicines support the relationship of trust that is essential for patients and treating healthcare professionals. The regulatory procedures set out for the authorisation of medicines and the subsequent safety monitoring of them once approved are guarantors of such trust. Using regulatory approved treatments and technologies according to the medical need of the patients, ensures the integrity of the regulatory system for medicines is not undermined.

We would draw attention to previous instances where the World Health Organisation has taken a stance against off-label use of medicines: Misoprostol is an approved medicine for ulcer treatment in more than 80 countries; however it is also used off-label in the management of elective medical and surgical abortion, miscarriage, induction of labour and postpartum haemorrhage. The most controversial use of misoprostol, according to the WHO, relates to its use in postpartum haemorrhage (PPH) and in 2011 the WHO advised a cautious approach regarding the advance community distribution of misoprostol during pregnancy and recommended rigorous research.\(^9\) In the 2011, WHO Expert Committee on the Selection and Use of Essential Medicines misoprostol was added to the EML for the prevention but not for the treatment of PPH, where oxytocin is not available or cannot be safely used.

**Conclusion**

For these reasons, EAASM believe it is essential that a choice of licensed treatment is available to patients on the EML so that they and their doctors can make fully informed decisions on the level of risk they wish to take. Patients and healthcare professionals can exercise this choice today, but the fact that the EML currently only lists an off-label treatment can be subject to confusion as to the choices they have open to them.

The World Health Organisation (WHO) defines patient safety as **“the prevention of errors and adverse effects to patients associated with health care.”**\(^10\) In this instance, the World Health Organisation and selection of treatments on the EML are essential constituents in embedding patient safety in healthcare policies around the world.

By failing to add a licensed product alongside an off-label product on the EML is by omission denying patients and prescribers the choice and obfuscating the option to treatment that uses a molecule specifically designed, tested, indicated and licensed for injecting in the eye. In the absence of any policing of the adherence to strict compounding guidelines, patients are at further risk of infection which can have devastating results.

Preventing harm to patients is challenging, but the risk of harm can be reduced by following regulations, guidelines and procedures already entrenched in most patient safety programmes.

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medicines are rightly among the tightest regulated products in the world. They are licensed, for specific conditions, only after exhaustive trials. Every effort should deployed to use approved treatments and technologies according to the medical need of the patient and any prescribing for treatment beyond approved use, should be done so only with the best medical interests of the patient in mind and with the patients’ fully informed consent.

EAASM believe the listing on the EML of licensed treatments is essential. A positive decision on the addition of Ranibuzumab to EML is an opportunity to embed a precedent acknowledging the right of patients and prescribers to choose for the safety profiles of licensed products. Failure to do so will undermine patients’ rights and Good Medical practice (GMP) and General Medical Council (GMC) prescription guidelines.

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