



## **Review of MHRA published statements on the supply and use of Avastin (bevacizumab) for intravitreal use**

The MHRA has been requested to review its published statements on the licensing status of Avastin when intended for intravitreal administration, in the context of the judicial review brought by Bayer and Novartis against the commissioning policy of 12 Clinical Commissioning Groups, in which judgment was given in September 2018.<sup>1</sup>

The MHRA was requested by the High Court to review “whether the process [of compounding bevacizumab] exceeds what is permissible for a given use to be ‘off-label’” – in other words whether the process creates a new product which requires its own marketing authorisation, in the absence of which the product is an unlicensed medicine, or not”.

The MHRA considers that further clarification of its published statements of 2009 and 2011 is necessary following the request from the court.

The MHRA has considered that its response to the request needs to draw a distinction between the functions regulated in the European scheme of medicines regulation on the one hand, and on the other, the clinical use of products within that marketplace. The medicines regulatory regime essentially legislates for the placing on the market of industrially produced medicinal products. The regime does not legislate how medicines are to be prescribed and used by healthcare professionals once they have been placed on the market. A prescriber may use a medicine outside the conditions of its marketing authorisation, and this is commonly referred to as ‘off-label’ use. The prescriber should be aware of their additional responsibility when prescribing ‘off-label’. Professional governance bodies have published advice to prescribers that should be taken into account.<sup>2</sup>

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<sup>1</sup> <https://www.judiciary.uk/wp-content/uploads/2018/09/bayer-and-novartis-v-nhs-darlington-cg-summary.pdf>

<sup>2</sup> For example, the General Medical Council, General Dental Council, Nursing & Midwifery Council or General Pharmaceutical Council

The MHRA has also published prescribing guidance in the context of medicines supplied as 'specials' and this should also be considered.<sup>3</sup>

The following text is provided to clarify the MHRA's position on the licensing regime that governs the placing of medicines on the market and to clarify and replace the guidance published in 2009 and 2011 concerning the licensing status of bevacizumab if intended to be placed on the market for intravitreal administration.

### **What is a licensed medicinal product?**

A licensed medicinal product is one which has a Marketing Authorisation (MA). An MA includes data supporting the quality, safety and efficacy of a medicine in the claimed indication for its use. An MA's "Summary of Product Characteristics" (SmPC) outlines, among other things, the indication(s), recommended dose(s), contraindications, special warnings and precautions for use on which the authorisation is based.

In addition, the SmPC describes the method of administration and conditions for safe storage of the medicine. In all, the SmPC describes the conditions in which the benefits of the medicine have been judged to outweigh the potential risks.

The medicines licensing regime ensures that a licensed medicine:

- has been assessed for safety, quality and efficacy
- has been manufactured to appropriate quality standards
- when supplied, is accompanied by appropriate product information and labelling

This regime is intended to ensure that ordinarily medicinal products are subject to a regulatory assessment of safety, quality and efficacy before being supplied and administered to a patient.

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<sup>3</sup> <https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials>

The licensing regime also provides for a system of pharmacovigilance (safety monitoring) to document and review the ongoing risks associated with the clinical use of a medicinal product; this is to ensure that rare adverse events which may not be identified in pre-approval clinical trials can be identified and assessed.

Unless exemptions apply (for example where there is a special clinical need), medicinal products must be the subject of an MA before being placed on the market and they may not be placed on the market otherwise than in accordance with the terms of their MA, including by manufacturers and wholesalers.<sup>4</sup> The term “sell or supply” is used in the Human Medicines Regulations 2012 but this is synonymous with the term “place on the market” which is used in European medicines legislation.<sup>5</sup>

### **What is ‘off-label’ use?**

The term ‘off-label’ is often used in an indefinite way; it can be used to capture a wide range of different activities in relation to the clinical use and administration of a licensed medicinal product in ways that are not described in the granted MA.

A prescriber may consider the use of a licensed product outside the conditions described in the SmPC. Examples of this include:

- the use of a licensed product to treat a disease (indication) which has not been included in the SmPC; or
- the administration of the licensed product by a route which has not been assessed for safety or efficacy (for example, oral administration of an injectable product).

The way in which a prescriber may choose to use or administer a medicinal product is not regulated in European medicines legislation; such legislation controls the manufacture and placing on the market of medicinal products.

In the UK, the Access to Medical Treatments (Innovation) Act 2016 defines ‘off-label’ use as the use of a licensed product:

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<sup>4</sup> Regulation 46 of the Human Medicines Regulations 2012.

<sup>5</sup> Preamble and various Articles of Directive 2001/83/EC as amended.

- “(a) for a purpose other than one for which its use is specified,
- (b) in relation to a person who is not within a description of persons for whom its use is specified, or
- (c) in any other way in which its use is not specified...”

In these circumstances, “specified” means as described in the product’s MA.

A 2017 report<sup>6</sup> published by the European Commission’s Expert Group on Safe and Timely Access to Medicines (the “STAMP Expert Group”) has the following definition for ‘off-label’ use:

“...Off-label use refers to any intentional use of an authorised product not covered by the terms of its marketing authorisation and therefore not in accordance with the SmPC. This may for example be the use for a different indication, use of a different dosage, dosing frequency or duration of use, use of a different method of administration, or use by a different patient group (e.g. children instead of adults) ...”

The European Medicines Agency defines ‘off-label use’<sup>7</sup> as:

“Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration.”

The term ‘off-label’ use of a product is predicated on the approval of a MA for that product and refers to how practitioners use that product when such use is not included in the MA and after the product has been placed on the market.

### **What is an unlicensed medicine?**

The term “unlicensed” may be used in relation to a medicinal product which is not covered by an MA, such as a medicinal product which is manufactured to meet a special clinical need. However, as noted above, medicines legislation primarily regulates the placing of medicines on the market, rather than clinical decisions on the use to which medicines are put. The placing on the market of a medicine in the

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<sup>6</sup> [https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp6\\_off\\_label\\_use\\_background.pdf](https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp6_off_label_use_background.pdf)

<sup>7</sup> <https://www.ema.europa.eu/en/glossary/label-use>

absence of a marketing authorisation or when intended for use in a way that is not included in its marketing authorisation, would also be unlicensed. Medicines may not be placed on the market in these circumstances unless a specific exemption provided in the legislation is applicable.

### **What is expected when healthcare professionals prescribe 'off-label'?**

There are clinical situations when the use of a licensed product 'off-label' may be judged by a prescriber to be the only way to meet the clinical needs of a certain patient. Such practice is particularly common in certain areas of healthcare; for instance, in paediatrics where difficulties in the development of age-appropriate formulations means that many medicines administered to children are used 'off-label'.

The prescribing of medicines is generally governed by professional standards and guidance published by the relevant UK healthcare professional regulators. The MHRA's Guidance Note 14 contains "Guidance on the hierarchy for the use of unlicensed medicines", which refers to 'off-label' use.

Prescribers have a responsibility to help monitor the safety of medicines in clinical use through submission of suspected adverse drug reactions to the MHRA and Commission for Human Medicines via the Yellow Card Scheme.<sup>8</sup> Such reporting is equally important for those products used 'off-label' as it is for those that are licensed and used within the terms of their MA.

Prescribers should understand the risks associated with 'off-label use'. These risks may include:

- unforeseen adverse reactions
- issues with product quality
- incomplete or discrepant product information or labelling

### **What is the MHRA's current (2019) position on the intravitreal use of Avastin (bevacizumab)?**

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<sup>8</sup> <https://yellowcard.mhra.gov.uk/>

Avastin's use in the ophthalmology setting has not been subject to a formal regulatory assessment for safety, quality and efficacy and no relevant MA covers its use in this way. The use of Avastin by practitioners for an indication, by a route of administration and posology which differ from those described in the product's approved SmPC, and after the product has been placed on the market, would be considered 'off-label' use.

The MHRA is aware that the processing of bevacizumab for intravitreal use may involve repackaging of the licensed medicine (a "concentrate for solution for infusion") to produce multiple small volume aliquots, usually presented in plastic syringes. This activity does not in itself make the product "unlicensed"; the consideration of a product's status as "unlicensed" must be taken in the circumstances of that product being placed on the market. It is acknowledged that the additional guidance published in 2011 was not sufficiently clear on this point.

If the single dose syringes for intravitreal use were to be placed on the market, such a medicinal product would need to be the subject of a new MA (or be covered by an exemption from the need for an MA such as a special clinical need) because the product:

- is intended for the treatment of a different indication, by a different route of administration and at a different dose from the authorised medicinal product
- has a different product presentation and container closure system
- is intended to be a different pharmaceutical form (a "solution for intravitreal injection")
- would need to have a different SmPC, Patient Information Leaflet and product labelling

Whether or not a product is placed on the market is a matter to be considered in the circumstances of each case.

A CCG policy of favouring the use of compounded bevacizumab for the treatment of wet AMD is currently the subject of a legal challenge<sup>9</sup>. This guidance will be reviewed, and updated if necessary, following the conclusion of those proceedings.

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<sup>9</sup> <https://www.judiciary.uk/wp-content/uploads/2018/09/bayer-and-novartis-v-nhs-darlington-ccg-judgment.pdf>.  
The judgment is being appealed to the Court of Appeal, which will hear the matter in November 2019.