**Abstract**

There are many medicinal products that, although having shown efficacy and safety in different ophthalmological indications, they are not authorized or commercially available for ophthalmic administration. This implies, on one hand, that they must be used according to legislation that regulates the availability of medicines in special situations and, on the other hand, that they must be prepared in the pharmacy services for ophthalmic administration, according to quality criteria to ensure its effectiveness, stability and sterility. This document gathers the consensus between the Spanish Society of Ophthalmology and the Spanish Society of Hospital Pharmacy about these selected preparations which have shown enough evidence in their efficacy and safety for their ophthalmic use (off label) and ophthalmic administration. This document includes recommendations about its use according to the current legislation. In addition, with the aim of harmonizing the preparation of intraocular injections in the hospital pharmacy services, general recommendations are set in this document to ensure the compliance with standards established in the Spanish Guideline for Good Pharmaceutical Preparations complianced with standards established in the hospital pharmacy services, for ophthalmic administration, according to quality criteria to ensure its effectiveness, stability and sterility. This document includes recommendations about its use according to the current legislation. In addition, with the aim of harmonizing the preparation of intraocular injections in the hospital pharmacy services, general recommendations are set in this document to ensure the compliance with standards established in the Spanish Guideline for Good Pharmaceutical Preparations.

**Keywords**

Ophthalmic solutions; Consensus; Macular Degeneration; Endophthalmitis; Intraocular Injections; Intravitreal Injections; Pharmaceutical Preparations; Keratitis.

**Palabras clave**

Colirios; Consenso; Degeneración macular; Endoftalmitis; Inyecciones intraoculares; Inyecciones intravitreas; Preparaciones farmacéuticas; Queratitis.
Preparation Practices of Medicinal Products in Hospital Pharmacies. These recommendations include sections such as the area of preparation, material, technique, packaging, stability, quality control, prescription and traceability of intravitreal preparations.

Introduction

Currently, the pharmaceutical industry does not offer forms that cover all the needs of ophthalmological treatment. Thus, this therapeutic gap should be addressed by the centralised preparation of such forms in hospital Pharmacy Services (PS) using authorised medications for other indications or administration routes.

The use of medicines under conditions other than those described in the summary of product characteristics is regulated by the Spanish Royal Decree (RD) 1015/2009, which defines this approach as “the use of medicines under conditions other than those authorized” (Spanish acronym: UMCDA). Chapter III, article 13 of the RD establishes the requirements for such use and includes the following statement:

- The doctor must provide a sound justification in the clinical history of the need to use the medication.
- The responsible doctor must obtain the consent of the patient according to Spanish Law 41/2002 on patient autonomy.
- Suspected adverse reactions must be notified according to the provisions of RD 1344/2007 regulating the Pharmacovigilance of Medicinal Products for Human Use.
- Restrictions that have been established related to the prescription and dispensation of the medication and the therapeutic protocol of the centre will be respected.
- The fact that the UMCDA may be linked to a protocol prepared by the health centre serving the patient involves the need to carefully assess the available evidence on each medication for each of the indications for which it is intended.

Furthermore, in 2011, in resolution CM/ResAP (2011)12, the Council of Europe aimed to standardise the quality of medicinal products, and recommended the development of practical guidelines on drug preparation to avoid differences in quality and safety between medications prepared in pharmacies and those manufactured on an industrial scale. Thus, in 2012, in its adaptation to Spanish regulations, RD Law 16/2012 was published on urgent measures to guarantee the sustainability of the National Health System and improve the quality and safety of its services13. RD Law 16/2012, article 7 establishes that the PSs in which these operations are conducted must guarantee adherence to the good practice technical guidelines. Therefore, the preparation of medicines must meet the quality criteria outlined in the Good Practice Guidelines on Pharmaceutical Preparation (Spanish acronym: GBPP)4 in order for them to be dispensed in a form ready to be administered under the required conditions after risk assessment and assignment of the necessary quality criteria. The preparation of pre-filled syringes ready to use is included as one of the operations of the manipulation and adaptation of preparations5. Specifically, the division of very high-cost therapeutic substances from a commercial single-use vial into multiple individual doses is frequently performed by hospital PSs in the attempt to minimize the high economic impact of these therapies.

Based on the risk assessment, preparations for intraocular administration should be prepared centrally in PSs in a laminar flow cabinet (LFC) with a controlled environment given the possibility of patients experiencing adverse effects caused by the contamination of these types of preparations6. However, although there are many general recommendations for the preparation of these types of products, to date there is no unanimous consensus on specific techniques to maximize benefits, while obtaining the largest number

Table 1. Proposed protocol for the use of ophthalmic drugs under conditions other than those authorized

| Objective: Define the treatment and indication. |
| Scope and exclusions: |
| **Scope:** Patient with the pathology to be treated and setting. |
| **Exclusions:** Contraindications to treatment and other contraindications if needed. |
| Related documentation and references. |
| Definitions: |
| - Define the use of medicines under conditions other than those authorized by Royal Decree 1015/2009, which regulates the availability of medicines in special situations. |
| - Define or include explanations of other terms that are used in the body of the document if needed. |
| Responsibilities. |
| Development of the procedure: |
| **Introduction and justification:** Cite the regulations on the use of medicines under conditions other than those authorized and justify the need to create the document. |
| **Diagnosis and establishment of treatment:** |
| - Criteria for inclusion in each therapeutic step. |
| - Evidence of the efficacy and safety of the treatment. |
| - Description of the treatment: administration route, dose, schedule, place (e.g., operating room), previous or subsequent relevant measures, periodicity of revisions, and so on. |
| - Duration of treatment. |
| - Criteria of refractoriness to treatment. |
| **Prescription and dispensation regulations.** |
| Flowchart. |
| **Management of the implementation of the procedure:** Management/Commission/Working group to sponsor the protocol, those who have prepared it, date of coming into force, dissemination, date of review, indicators for the assessment of the objectives, and those responsible for their measurement. |
| Annexes: |
| - Model of informed consent. |
| - Information for the patient (in the case of external patient). |
of individual syringes possible and ensuring the sterility, stability, and effectiveness of the doses prepared.

The objectives of this document are: (1) to establish which drugs and under what conditions there is sufficient pharmaceutical and clinical evidence to support their use other than that described in the summary of product characteristics in order to cover the most common therapeutic gaps in ophthalmological treatment, and thus facilitate the development of care protocols in health centres; and (2) to establish a set of general recommendations for the preparation of intraocular injections that are useful for the health personnel involved in their preparation and that increase patient safety.

Methods

This document was developed by a working group comprising members of the Spanish Group of Pharmaceutical Compounding of the Spanish Society of Hospital Pharmacy (Spanish acronym: SEFH) and members appointed by the board of the Spanish Society of Ophthalmology (Spanish acronym: SEO). The document was developed in several phases:

- The members of the Spanish group of Hospital Pharmacy Compounding shared information on the ophthalmological medications they most frequently prepared in their own health centres, their indications, and the galenic and clinical evidence on which they were based.
- After drawing up an initial list, it was reviewed by the SEO assessment group for possible corrections or the inclusion of new preparations.
- The list reviewed by the SEO underwent a final literature search of the galenic evidence related to the selected preparations using PubMed. Thus, the following keywords were used: ophthalmic solutions, drug stability, keratitis, endophthalmitis therapy, intravitreal injections, intraocular injections, and drug compounding.
- Members of the Spanish Group of Hospital Pharmacy Compounding used the GBPP as a reference to establish recommendations on the preparation of intraocular injections. This group also used PubMed and other electronic literature sources to conduct a literature search using the following keywords: intraocular injections, intravitreal injections, pharmaceutical preparations, drug compounding, drug stability. In this way, a draft recommendation was created on the characteristics of the environment, material required, preparation technique, shelf-life, and quality control of the intraocular preparations. This draft was shared among the members for its review and for further contributions taking into account the expertise of each professional in each of the sections mentioned.

### Table 2. Preparations of Eye Drops, Indications and Posology, and Recommended Dosage

<table>
<thead>
<tr>
<th>PREPARATION</th>
<th>INDICATIONS</th>
<th>RECOMMENDED DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcysteine 50-100 mg/mL eye drops</td>
<td>Conditions that require lysis of mucopolysaccharides of the tear fluid, mucolytic activity on the tear fluid, such as burns and dry keratitis.</td>
<td>Instil in lower conjunctival sac, 1 drop several times a day as needed.</td>
</tr>
<tr>
<td>Amikacin 50 mg/mL eye drops</td>
<td>Keratitis and other severe ocular infections (mainly of the anterior ocular segment) sensitive to this medication or in empirical antibiotic therapy.</td>
<td>Instil in lower conjunctival sac, 1 drop several times a day as needed. Typically start at 1 drop per hour.</td>
</tr>
<tr>
<td>Bevacizumab 5-25 mg/mL eye drops</td>
<td>Processes involving unwanted neovascularization of the anterior ocular segment, especially the cornea.</td>
<td>Instil in lower conjunctival sac, 1 drop several times a day as needed. Typically 1 drop every 6 hours.</td>
</tr>
<tr>
<td>Cefazidime 50 mg/mL eye drops</td>
<td>Keratitis and other severe ocular infections (mainly of the anterior ocular segment) sensitive to this medication or in empirical antibiotic therapy.</td>
<td>Instil in lower conjunctival sac, 1 drop several times a day as needed. Typically start at 1 drop per hour.</td>
</tr>
<tr>
<td>Cyclosporine 0.5-20 mg/mL eye drops</td>
<td>Anterior segment ocular disease involving an autoimmune response requiring suppression, such as dry eye, allergic conjunctivitis, and graft-versus-host disease. Higher concentrations are reserved for severe conditions.</td>
<td>Instil in the conjunctival sac fund, 1 drop several times a day as needed. Typically 1 drop every 6-8 hours.</td>
</tr>
<tr>
<td>Chlorhexidine 0.02% eye drops</td>
<td>Anterior segment ocular infections due to pathogens sensitive to this medication, such as keratitis caused by Acanthamoeba.</td>
<td>Instil in lower conjunctival sac, 1 drop several times a day as needed. Typically start at 1 drop every 1-2 h.</td>
</tr>
<tr>
<td>Interferon alfa-2B 1 million IU/mL eye drops</td>
<td>Used for the treatment of corneconjunctival ocular surface squamous neoplastic lesions, conjunctival papillomas, and recurrent pterygium.</td>
<td>Administer 1 drop 4 times a day until the lesion disappears.</td>
</tr>
<tr>
<td>Mitomycin 0.2 and 0.4 mg/mL eye drops</td>
<td>Anterior segment ocular disease involving accelerated mitosis, such as conjunctival tumours. Also postsurgical use to avoid excessive fibrosis/postoperative scarring, such as after pterygium surgery, dacryocystorhinostomy, or glaucoma surgery. Two concentrations are available depending on the aim of treatment.</td>
<td>Instil in lower conjunctival sac, 1 drop several times a day as needed.</td>
</tr>
<tr>
<td>Autologous serum 20%-50% eye drops</td>
<td>Anterior segment ocular disease, such as neurotrophic keratitis, or following keratoplasty requiring the use of trophic substances or growth factors present in blood plasma.</td>
<td>Instil in lower conjunctival sac, 1 drop several times a day as needed.</td>
</tr>
<tr>
<td>Vancomycin 50 mg/mL eye drops</td>
<td>Prevention and treatment of keratitis and other severe ocular infections (mainly of the anterior ocular segment) caused by pathogens sensitive to this medication or in empirical antibiotic therapy.</td>
<td>Instil in lower conjunctival sac, 1 drop several times a day as needed. Typically start at 1 drop per hour.</td>
</tr>
<tr>
<td>Voriconazole 10 mg/mL eye drops</td>
<td>Ocular surface infections caused by fungi sensitive to this medication.</td>
<td>Instil in lower conjunctival sac, 1 drop several times a day as needed. Typically start at 1 drop per hour.</td>
</tr>
</tbody>
</table>
this phase, it was decided to include aspects related to syringe packaging, prescription, and traceability of the samples.

- Finally, the document was reviewed and endorsed by the SEO assessment group within the framework of the SEO-SEFH collaboration agreement. The document was signed by the board of the SEO on November 16, 2017.

**Results**

**Recommendations on the use of ophthalmic medications**

As mentioned, the use of medications under conditions other than those authorized involves respecting the established restrictions on the prescription and dispensation of the medications and following the health care protocol of the centre. This protocol (or protocols if it has been decided to design one for each active ingredient) must be agreed upon by the services involved in the use of the medication and approved by the Pharmacy and Therapeutics Commission and by the management of the health centre.

Table 1 shows a proposed protocol for the use of ophthalmic drugs under conditions other than those authorized.

In each application the prescribing physician provides a sound justification in the clinical history of the need to use the medication, inform the patient of the potential benefits and risks, and obtain their informed consent.

Tables 2 and 3 provide examples of eye drops and intracocular injections, respectively, their indications (unauthorized), and the most common posology.

**General recommendations on the preparation of intraocular preparations**

Annex 1 shows the recommendations for the preparation of intraocular preparations. This annex provides information on the following aspects: preparation area, characteristics of the material, preparation technique, packing, shelf-life, quality control, prescription, and traceability.

Depending on the type of preparation, special requirements will be taken into account for the preparation of terminal sterilization products or for aseptic preparation as outlined in the GBPP.

**Conclusions**

There is ample clinical evidence supporting the use of the drugs selected in this study for ophthalmic use, although the health authorities do not recognize such use in the majority of cases.

From a legal point of view, these preparations would be included in what is known as the use of medicines under conditions other than those authorized. Their use should be incorporated in the health care protocols agreed by the ophthalmology services and approved by the Pharmacy and Therapeutics Commission and the centre’s management body.

There is also galenic evidence supporting the preparation of these medications such that they can be administered by the ophthalmic route in the form of eye drops or intraocular injections.

Ophthalmic medications must be prepared in accordance with the guidelines established in the GBPP. In addition, the specific recommendations on intracocular preparations established in this document will help to standardize and facilitate the preparation of these medications in hospital PSs, thereby making these types of preparations equally accessible to all patients.

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**Table 3. Preparations, Indications, and Recommended Dosage**

<table>
<thead>
<tr>
<th>PREPARATION</th>
<th>ADMINISTRATION ROUTE</th>
<th>INDICATIONS</th>
<th>RECOMMENDED DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Intravitreal injection</td>
<td>Treatment of intraocular diseases involving neovascularization, such as age-related or myopic macular degeneration, diabetic retinopathy, retinal venous obstruction, neovascular glaucoma. Also to prevent intraocular bleeding prior to vitrectomy or glaucoma surgery.</td>
<td>Typically administered in a single dose and repeated every 30 days if needed.</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>Intravitreal injection</td>
<td>Prevention and treatment of severe intraocular infections (endophthalmitis) by pathogens sensitive to this antibiotic.</td>
<td>Typically administered in a single dose and repeated at least every 24 hours.</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>Subconjunctival injection</td>
<td>To avoid excessive scarring (e.g., postoperative fibrosis following glaucoma or pterygium surgery).</td>
<td>During surgery, it is applied with a surgical sponge to the sclera for 0.5-5 minutes. After surgery, it is applied in the form of subconjunctival injections (0.1 mL) repeated at least every 24 hours until the treatment aim is achieved.</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Intracameral injection</td>
<td>Treatment of intraoperative floppy iris.</td>
<td>Typically administered as an intracameral injection of 0.1 mL phenylephrine at the end of the intervention.</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Subconjunctival injection</td>
<td>To avoid excessive scarring (e.g., postoperative fibrosis following glaucoma or pterygium surgery).</td>
<td>During surgery, it is applied with a surgical sponge to the sclera for 3-5 minutes. After surgery, it is applied in the form of subconjunctival injections (0.1-0.25 mL) repeated at least every 24 hours until the treatment aim is achieved.</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Intravitreal and intracameral injection</td>
<td>Prevention of postoperative infection and treatment of severe intraocular infections (endophthalmitis) by pathogens sensitive to this antibiotic.</td>
<td>Typically administered as an intracameral injection of vancomycin at the end of intervention. In the case of endophthalmitis, this can be administered via the intracameral or intravitreal route in a single dose or repeated at least every 24 hours.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Intravitreal injection</td>
<td>Prevention and treatment of severe intraocular infections (endophthalmitis) by fungi sensitive to this antibiotic.</td>
<td>Typically administered in a single dose and repeated at least every 24 hours.</td>
</tr>
</tbody>
</table>
Annex 1. Recommendations for the Compounding of Intraocular Preparations

1. PREPARATION AREA

- Intraocular preparations should be prepared in a horizontal or vertical Laminar Flow Cabinet (CFL) according to the risk assessment of the medication in a controlled environment: in a EU-GMP grade A cabinet (or ISO 5 class according to the UNE-EN ISO 14644-1 at rest or in operation) and a grade B working area environment (or class ISO 5 at rest) if starting with non-sterile material, or a grade C working area environment (or ISO class 7 at rest) if all starting materials are sterile. During aseptic preparation it is also possible to work in a positive pressure pharmaceutical isolator (if the substance is not hazardous) in a grade D environment (or ISO 8 class at rest)6.

- The presence of materials that can release fibres should be minimized in clean areas, and so the use of sterile drapes instead of gauze is recommended.

2. MATERIAL

- The materials used, such as types of needle, filters, or syringes, will be suitable for the starting substances and the type of preparation, while always checking for their compatibility. For example, during the process of syringe preparation, the filtration of bevacizumab should be avoided6.

- In the case of the preparation of terminal sterilization products, 0.22-μm filters suitable for the type of solution to be sterilized should be used. Due to risks inherent to the intraocular route, double sterilizing filtration should be performed before filling the final container4.

- In the case of starting with sterile substances, and only if the substance is compatible, 5-μm particle filters should be used to prevent glass particles from the ampoules or elastomers from the vials from entering the preparation. Providing the substance is compatible, 0.22-μm filters can be used prior to filling the final container in order to increase the sterility of the preparation and thus its safety. Particles would also be removed during this sterilizing filtration process.

3. PREPARATION TECHNIQUE

- In the case of preparations in which a prior dissolution or dilution of the medication at a certain concentration is needed for intravitreal administration, such as in the preparation of antibiotics, syringes will be filled through the hub of the syringe with the syringe already loaded with the solution, and filtered using the appropriate filter which is compatible with the substance. The resulting syringes will be capped with sterile plugs and the intravitreal administration needles will be attached to the syringes in the operating room.

- If divided doses obtained from high-cost biological medication vials are required, a possible approach would be as follows:

  1) Leave the vial to rest for a few seconds in an upright position on the surface of the cabinet to allow all the medication to slide down the walls to the bottom of the vial.

  2) Extract the medication in the syringe through a needle with a suction filter ensuring compatibility between the substance and the filter membrane.

  3) Load the volume of medication agreed upon with the ophthalmology service into fixed-needle dead-space-free syringes. The size of the syringe and needle will be that agreed upon with the ophthalmology service because the ophthalmologist will directly administer the medication with this syringe via the fixed needle. The technique would be as follows: Using the fixed-needle dead-space-free syringes, directly extract the required volume through the hub of the syringe loaded with the medication. In this case, precautions must be taken to prevent the microneedle of the dead-space-free syringe from rubbing any surface of the syringe containing medication. Extraction through the hub of the dead-space-free syringes can be facilitated by the use of a pipette holder to hold the syringe loaded with the medication in an upright position.

- The vials of the monoclonal antibodies must not be shaken and the medication should be carefully transferred to the syringe to avoid protein aggregation. It should be ensured that there is no turbidity because this would indicate aggregate formation6.

- The formation of bubbles and the introduction of air into the syringes should be avoided because this can lead to protein instability26.

4. PACKAGING

- Prepared syringes should never be labelled directly on the barrel of the syringe, and they should be packaged inside the LFC in sterile self-sealing bags which will be labelled.

- Depending on the particular working method (procedure, personnel involved in opening the bags and taking the syringe to the operating room), it could be advisable to use a double sterile bag to package each syringe. That is, each bag containing the syringe will be placed inside a second sterile bag. In this case, this second bag will be the one to be labelled. The need for the second sterile bag must be previously agreed with the ophthalmology service.

- Finally, all labelled bags will be packaged in a lightproof bag for conservation and transportation.

- It is highly recommended that auxiliary support staff are available in the sterile area to check the volume of the syringe, bag labelling, and so on, thus preventing the person preparing the syringes from taking his/her hands away from the sterile areas and touching non-sterile material.

5. SHELF-LIFE

- According to the GBPP, medium-risk preparations prepared in a LFC with a controlled environment have a microbiological shelf-life of 9 days in a refrigerator (2 °C – 8 °C) and 45 days in a freezer (≤ -20 °C), provided that their physical and chemical stability is not less than the aforementioned periods and that the substance can be kept in a refrigerator or freezer4.

- Likewise, when using open systems or preparing non-sterile products or materials, high-risk preparations prepared in a LFC with a controlled environment have a microbiological shelf-life of 3 days in a refrigerator (2 °C – 8 °C) and 45 days in a freezer, provided that their physical and chemical stability is not less than the aforementioned periods and the substance can be kept in a refrigerator or freezer4.

- Biological medicines should not be frozen because they may undergo alterations in their molecular structure26. It is recommended that the divided doses should be prepared closer to the time of administration.

- Shelf-lives longer than those established in the GBPP may be assigned when:

  - They are documented in a high-impact publication and the formulation is the same as that documented in the literature4;
  - Or when the responsible pharmacist performs the final sterility test to validate the preparation and routinely performs periodic tests to ratify the assigned validity4.
Annex 1 (cont.). Recommendations for the Compounding of Intracocular Preparations

6. QUALITY CONTROL

- All starting materials and packaging materials must undergo visual inspection before use to ensure that they meet all specifications1.

- Sterility test: When preparing a batch of more than 25 units of high-risk preparations, the batch must undergo microbiological analysis. In high-cost preparations, it is not economically feasible to waste 1 or more units in order to reach the volume needed to inoculate the culture medium. In these cases, other measures are applicable to ensure the continuous quality of the preparation process, such as validating the aseptic technique by simulating the preparation with a culture medium that replaces the medication, preparing it with the same procedure27.

- If a product is prepared for administration to a single patient, the only aspects that have to be checked are its appearance and the final clarity of the finished product3. The PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments28 recognizes that it is unnecessary to perform sterility tests in individual extemporaneously prepared medicinal products per patient, because this process would involve handling the final product.

7. PRESCRIPTION

- It is recommended that these substances are prescribed for outpatients using the computer application available to the hospital. This prescription will also serve to confirm the scheduling of surgery and for managing dispensing per patient.

8. TRACEABILITY

- With the agreement of the ophthalmology service, and in order to help ensure the traceability of the preparations, it is recommended to send a label identifying the batch and shelf-life of the preparation so that it can be attached to the patient’s medical record.

9. OTHER OBSERVATIONS

- An alternative technique for preparing divided doses from vials of high-cost biological medicines would be to previously extract the plunger of the dead-space-free syringes and load through the inlet part of the plunger. In this case, precautions should be taken when replacing the plunger and extracting air from the syringe to ensure that medication is not wasted. It is essential to ensure the absence of bubbles in the preparations.

- The use of a decapper to remove the metal top of the vial would prevent the release of its particles into the contents of the vial and the needle, and would also contribute to better use of the vial, because this approach would prevent wastage of medication on the walls of the rubber stopper29.

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