Policy document MEB 47

Test criteria for combination packages

1 Contents

2 Abbreviations

Coordination Group for Mutual Recognition and Decentralised procedures - Human	CMDh
Fixed dose combination	FDC
Notice to Applicants	NtA

3 Introduction

3.1 Definition of a combination package

A combination package is a package that contains more than one medicinal product and is marketed under a single trade name and has a single marketing authorisation. The qualitative or quantitative compositions of the individual products are different and they are administered at the same time or sequentially. In turn, the individual components in the packaging can be fixed dose combinations (FDCs) too, as is the case for example with oral contraceptives or a fixed combination of an ACE inhibitor with a diuretic.

The 'CMDh questions & answers applications for marketing authorisation' (http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_268_2012_Rev05__2016_01_clean1.pdf) provide the following definition of a combination package:

There is no definition of a combination package in Directive 2001/83/EC, but the CMDh has agreed on the following understanding of a combination package: A combination package is a package that contains more than one medicinal product marketed under a single tradename, intended to be used in a medical treatment where the individual medicinal products are simultaneously or sequentially administered. The combination packages should be distinguished from a fixed combination which is a combination of active substances within a single pharmaceutical form.

The MEB has adopted a policy for combinations of medicinal products with auxiliary devices that is comparable to that for combination packages of medicinal products.

3.2 European admission requirements for combination packages

'Notice to Applicants (NtA), Vol. 2A, Procedures for marketing authorisation, Chapter 1' (http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf) also mentions combination packages:

The combination of active substances whereby active substances are included in separate pharmaceutical forms and presented in a combination pack cannot be considered as fixed combination. In very exceptional circumstances, which must be considered on a case-by-case basis, the marketing of distinct medicinal products in the same package may be indispensable for public health reasons. Such reasons cannot be related to convenience or commercial purposes.

The document 'CMDh questions & answers applications for marketing authorisation' states the following:

In principle Member States could accept a combination package if there are strong arguments for the provision of a combination package with respect to benefit to public health or where the use of a combination pack is more user-friendly for the patient or healthcare professional. Commercial reasons are not considered a valid justification for the provision of a combination package.

The MEB follows the NtA in using the concept of 'convenience'. Convenience is not seen as a pharmacotherapeutic rationale. Convenience can therefore only be used as a supporting argument for the combination of the components.

4 Purpose and scope

This document contains test criteria for assessing combination packages. The criteria as defined in Chapter 1 of Volume 2A of the NtA (Notice to Applicants) and the above-mentioned 'CMDh questions & answers' are covered in more detail in this document.

The combination of a medicinal product with an auxiliary device must comply with the 'required condition'.

This policy document does *not* apply to FDCs.

5 Test criteria for combination packages of medicinal products

The criteria help in assessing combination packages; the criteria are not described in very precise terms, so the MEB can form an opinion in specific cases that arise about the question of whether it thinks that the conditions for granting a marketing authorisation for the combination package have been met. A combination package will be accepted if it complies with the 'required conditions' plus at least one 'special condition'.

5.1 Required condition

A product that is to be approved must meet the following required condition:

1. There is a **pharmacotherapeutic rationale** for the combination of the components. The components of the combination package all contribute to the treatment of the indication. This may for instance be demonstrated by the combined use of the individual components being explicitly stated in the SmPC of one of the monocomponents or it may also be evident from other arguments in the dossier. This condition is also deemed to have been met if one of the components is active not on its own, but instead only in combination (a pharmacokinetic booster, for example).

   The approach based on the pharmacotherapeutic rationale of a combination package is oriented towards the approach to FDCs described in the 'Guideline on clinical development of fixed combination medicinal products'.

5.2 Special conditions

A product that is to be approved must also always meet at least one of the following conditions:

2. **Problematic instructions for use.** The package supports instructions for use that are more difficult to carry out reliably for the separate products.
3. **New indication.** At least one of the components has not been authorised separately, or at least one of the components (as a separate product) has not been indicated for the condition that the combination package has been indicated for.
4. **Course of treatment.** The combination package provides a full course of treatment of a specific indication, for example *H. pylori* eradication. This argument weighs more heavily if the combination is only used for a short period.

5.3 General terms and conditions

The criteria stated below are not intrinsically sufficient reason to develop a combination package. However, if they are not met, it will be seen as a source of doubt as to the safety and relevance of the new combination package.

5. **No fixed dose combination.** It is not possible to replace the combination with an FDC; no such FDC exists and one cannot be developed either; the requesting party must state the reasons why such an FDC is not a possibility.
6. **Use at home.** All the components of the package can be used/administered by the patient. The advantages of a combination package are much less clear if the components have to be administered at a hospital or under the supervision of a healthcare professional. A combination package is undesirable if some components of the combination are used at home and others under supervision or at an institution, as this might result in unsupervised use at home.
7. **Absence of polypharmacy.** It must be reasonable to assume that the components of the combination package are the only medicinal products used by a proportion or significant proportion of patients for the indication or condition that the product is used for (unless a 'course of treatment' is involved). If polypharmacy is involved (with at least three products), combining just two products in a single package has little added value and may even have disadvantages, as it might confuse the user.
8. **The dosage regimen for the components in the combination package must be clear.**

6 Test criteria for combination packages of medicinal products plus auxiliary devices

Combinations of medicinal products with auxiliary devices require a clear pharmacotherapeutic rationale. A 'convenience kit' in which the package contains various auxiliary devices (available in a standard form) as well as the medicinal product is not acceptable. However, the combination of a medicinal product plus applicator specifically developed for the product and required for its administration is acceptable.

7 Stating the expiry date

A single expiry date should be stated on the outer packaging; the expiry date of the component with the shortest shelf life. However, the primary packaging of the individual components should state their own expiry dates.