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Committee for Medicinal Products for Human Use
Committee for Medicinal Products for Veterinary Use

Points to consider for the overall assessment of a supply shortage of a medicinal product for human and veterinary use due to GMP Non-compliance /quality defects

As soon as any disruption in the supply of a centrally authorised product (CAP) or a non-CAP becomes apparent, there are several facts that would need to be determined and evaluated. These include the cause, estimated duration and extend of shortage, availability of alternative treatments and adequate communication. The assessors shall complete the following report based on the preliminary/follow-up information available from the MAH of the affected product.

The assessment of a product shortage due to manufacturing or quality problem may require a cross-functional team of clinical, quality and pharmacovigilance experts.

Furthermore, the level of information and the subsequent assessment will vary on a case by case basis.

This template aims to provide points to consider for such an assessment.

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Table of Contents

1. Executive summary 3

2. Quality Discussion 3

2.1. Description of the GMP Non-compliance /quality defect 3

2.2. Remedial actions taken in order to resolve the GMP Non-compliance /quality defect 3

3. Clinical discussion 3

4. Pharmacovigilance 4

5. Benefit/risk assessment..... 4

6. Recommendations 5

7. Communication..... 5

8. List of questions to be addressed by the MAH 6

9. Follow-up assessment 7

Annexes 7

1. Executive summary

<The executive summary should provide a brief overview of the issue that has led to the shortage, and the current situation of the supply of the concerned medicinal product, as outlined in the sections below (description of the cause of shortage, type of medicinal product affected and its therapeutic use, possible corrective actions, availability of alternative treatments, final recommendations). The current benefit/risk assessment should be summarised, together with recommended actions and communications>

2. Quality Discussion

2.1. Description of the GMP Non-compliance /quality defect

<Describe the quality or GMP issue that is lead to the shortage and include a chronology of events:

Start and cause of the supply shortages and affected pharmaceutical forms or strengths of the medicinal product(s).

Duration of the shortage

Geographical impact of the shortage

Other products that are or could be affected by the shortage>

2.2. Remedial actions taken in order to resolve the GMP Non-compliance /quality defect

<Discuss if there is a need for recall of the affected batches in order to mitigate the clinical impact of the suspected quality issue.

Discuss any supervisory actions taken by authorities to verify the corrective and preventive measures taken, e.g. inspections, sampling and testing.

Discuss the adequacy of the corrective and preventative actions identified by the MAH to restore normal quality of the product as described by the marketing authorisation and/or GMP.

Discuss the effectiveness of any quality variations that have been submitted to implement the corrective actions or normalised the supply situation.>

3. Clinical discussion

<This section shall critically evaluate the situation in terms of the new batches released and if there is a need to recall the previous batches.

Discussion on the need to update the PI and the EPAR based on the clinical use of the product under shortage (i.e. with temporary treatment recommendations)

Clinical impact of the use of the alternative treatment, e.g. alternate formulations, lower strength, other medicinal product or procedures. The discussion should focus on the evaluation of the effectiveness of the original treatment recommendations.

Evaluation of any possible impact on the use of the concomitant medications prescribed with the medicinal product as part of the normal treatment regimen.

Clinical impact of the use of the defective product should also be discussed.

Impact on vulnerable populations, emergent specific adverse events, withdrawal symptoms, off-label use or other potential indications should be discussed, as identified during the use of the product under shortage conditions. >

If there was a switch to another product, discuss:

- *Ease of switching to alternates (of the same or a different product)*
- *Experience with "switching" patients/animals to alternative strengths, formulations, dosages of the same medicinal product*
- *Experience with "switching" patients/animals to alternative strengths, formulations, dosages of a different medicinal product*

Consideration for patients/animals remaining on the alternate therapy versus those switching back to the original medicinal product recommended once shortage is resolved should be discussed.

4. Pharmacovigilance

<Overview of the overall known safety profile of the medicinal product known to be affected taking into account all pharmacovigilance data, known or new safety signals, spontaneous reports and any additional data provided by the MAH or other sources.>

<If supply of defective product will be maintained, discuss the need for enhanced pharmacovigilance monitoring and reporting during the period. This should consider the adequacy of MAH proposals, including: frequency of monitoring; threshold levels for 'signals'; relevant ADR terms; and mechanisms for rapidly collating data from different Member States.>

<If patients/animals will be switched discuss the need to inform the MAH of the alternative to provide enhanced pharmacovigilance monitoring and reporting during the period.>

5. Benefit / risk assessment

<This section should summarise the main benefits and risks as identified in sections 2 to 4.>

POINTS TO CONSIDER:

Discuss the classification of the medicinal product as **Critical** or **Non-Critical**

Risks of non-supply of treatment

Risks related to the use of the defective/affected product: (probability of exposure to a contaminated product, and severity of clinical consequences)

Risk of reduced dose (if identified as feasible and appropriate)

The extent to which effective monitoring of risk (through enhanced pharmacovigilance) is feasible.

Benefit/risk of supply with an alternative product (if available)

Options to balance out identified risks *<setting criteria for a level of contamination that might be considered acceptable to maintain supply of a critical medicine, setting a level of evidence of harm*

beyond which batches should be withdrawn, setting a level of evidence of re-emergence of underlying disease in relation to reduced dose, etc.>

Discussion on recall, and replacement strategy.

6. Recommendations

<Based on the evaluated benefits and risks, this section should identify and discuss the appropriate (regulatory) action:

- *need for an inspection*
- *accelerated variation (e.g. addition of a new manufacturing site, modification of shelf-life of the remaining available product)*
- *initiation of a referral with a view to suspension, revocation or variation of the marketing authorisation.*
- *product replacement and recall of some or all batches*
- *diversification of supply may also need to be discussed*
- *need for additional/enhanced market surveillance testing within the OMCL network.*
- *need for additional/enhanced pharmacovigilance measures.*
- *Need for periodic status reports (quality, pharmacovigilance, clinical)*
- *other>*

7. Communication

RECOMMENDATION FOR COMMUNICATION BY EMA

<please refer to Annex III: "Communication by the European Medicines Agency on supply shortages of medicinal products">

POINTS TO CONSIDER:

The need/purpose of communication

Consequences of failure to communicate

Target audiences

Format *<DHPC, letter, press release, public communication, website announcement, etc.>*

Timing (aligned with MAH)

Core messages for all countries

Messages that may need tailoring at national level

Need for follow-up/updates (frequency)

COMMENTS ON COMMUNICATION PROPOSED BY THE MAH

<please complete as appropriate>

8. List of questions to be addressed by the MAH

The below are examples of questions that can be posed to the MAH in order to provide information for assessment of the shortage, in case such data have not been submitted already.

Product- and manufacturing- related question

a. Which batches, pharmaceutical forms, strengths, pack sizes are affected by the supply problem?

b. Which countries are experiencing supply interruption?

c. Is it likely that the supply problem will affect other countries in the near future?

d. Is a stock-out, or near stock-out situation likely to occur? If so, in which countries?

e. Provide a technical report of the problems in the manufacturing or quality area that means that has given rise to the possibility of a shortage. The MAH should be asked to provide analytical data and should discuss the relevance of the data. What is the root cause of the supply interruption and where in the manufacturing process does it occur?

f. What preventive and/or corrective actions has the company taken to avoid and/or resolve the shortage?

g. What is the current stock situation/member state? Are there any buffer stocks at distributor or hospital sites? Forecasted demand rates and estimated stock out dates should be provided. Discussion on the feasibility of stock rotation between member states to cover and any other measure to prevent the shortage should be requested.

h. What is the estimated lead-time before the product reaches out of stock level? Provide lead times and a timetable for (a) manufacture and supply utilising the batches in question and (b) manufacture and supply utilising new batches.

i. Considering the nature of the defect, what is the level of risk of the use of a defected product from the quality point of view? What is the threshold beyond which the quality defect has harmful effect on the patient and clinical use would deem inappropriate?

j. Is it possible to import the medicinal product (re-packging and re-labelling) from other EU member state to countries where shortage is evident? If so, how would this be handled?

k. Have all alternatives of improving the supply chain been explored? E.g. modification of manufacturing process, use of alternate manufacturers, etc.

l. What is the stock situation for other strengths or formulations of the medicinal product that could compensation for the supply interruption?

Clinical and therapeutic use of the medicinal product

a. How many patients/animals are currently treated with the affected medicinal product? Does this include the off-label use? Provide a detailed medical/veterinary risk assessment for

patients/animals who may have to receive a medicinal product manufactured using the affected batches.

b. Are there any specific or vulnerable sub-populations treated with the product, which should receive priority treatment?

c. Does the MAH have any data about the impact withdrawal of the medication on the patient/animal or on other concomitant treatments? Is there a need for a “step-by-step” withdrawal?

d. How feasible is it to find and switch to therapeutic alternatives? Does the MAH have any experience?

e. Can the MAH provide any date on a “restricted” use of the medicinal product, e.g. lowered dose, reduced administration frequency, interruption of the treatment?

f. Does the MAH foresee a need for educational material for the treating physicians/veterinarians and/or patients/end-users (DHPC, communication plan) in order to effectively implement any temporary treatment recommendations? If so, these should be provided.

g. What is the time span without treatment, during which no harm to the patient/animal can be expected?

h. Are there any on-going clinical trials that would be affected by the shortage (tested product, active comparator)?

9. Follow-up assessment

<This section should be used to assess the responses of the MAH to the LoQ>.

Annexes

Annex I: Criteria for classification of critical medicinal products for human and veterinary use

Annex II: Resources for issuing treatment recommendation during shortages of medicinal products

Annex III: Communication by the European Medicines Agency on supply shortages of medicinal products