10 October 2013
EMA/531390/2012
Patient Health Protection

# Proposal for communication on medicinal product supply shortages and recalls of medicines

## 1. Introduction

Short and long-term shortages of medicinal products have been a global problem for the past decade and over the last few years it has also increasingly affected the EU. Past shortages have affected all classes of medicines and included injectable chemotherapy agents, anaesthetic agents, intravenous nutrition and electrolyte products, enzyme replacement products and radiopharmaceuticals. The shortages of the enzyme replacement therapies for Fabry's disease and Gaucher's disease, Fabrazyme and Cerezyme, as well as the chemotherapeutic agent, Caelyx, are examples of recent high profile long-term shortages that affected the EU. Causes of shortages can be wide and varied, and include manufacturing problems, shortages of raw materials, regulatory issues (GMP non-compliance), labour disruptions and changing market incentives. Shortages may lead to numerous consequences for patients and healthcare professionals such as changes in treatment recommendations, and the set-up of patient allocation programs (Myzozyme, Cerezyme and Fabrazyme). They can have detrimental effects on patient care as they can lead to medicines rationing, delaying critical treatments, and utilising alternatives which can be less efficacious or which may increase the risk of medication errors due to unfamiliarity with the new regimen; they can also lead to adverse events caused by unexpected drug-drug interactions and suboptimal treatment outcomes.

The gravity of shortages has caused reactions from specialists and from governmental agencies around the world. In the USA, in the face of the rising incidence of medicine shortages new legislation and policies have been implemented to prevent, identify, and correct them. They include a broadening of the reporting requirements for potential shortages, acceleration of reviews of new applications for marketing of generics, annual reports on shortages by the US Food and Drug Administration (FDA) to Congress, the establishment of a medicine shortage list and a task force to "develop and implement a strategic plan" to enhance the FDA's ability to prevent and mitigate medicine shortages.[1] In addition leaders from key health care stakeholder organisations such as the American Society of Health System Pharmacists (ASHP), the American Society of Anesthesiologists (ASA), and the Institute for Safe-Medication Practices (ISMP), have made a coordinated effort to address the critical issue of medicine

[1] http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm313121.htm

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shortages by publicly conveying the seriousness of the crisis and potential solutions.[2] More recently the European Haematology Association (EHA), the American Society of Hematology (ASH), and the European Cancer Patient Coalition (ECPC) held a joint symposium in June 2012 and issued a common call for action in an effort to mitigate shortages of haematology medicines in Europe, the United States and around the world.[3] In September 2011, the Council of the International Pharmaceutical Federation called on all stakeholders, including governments, pharmaceutical manufacturers, pharmacy wholesalers, pharmaceutical purchasing agencies, medical insurers, pharmaceutical regulators and the pharmacy profession to urgently evaluate issues leading to shortages and work to ensure continuity of medication supply so that appropriate treatment for patients can be initiated and maintained.[4]

In Europe, the European Association of Hospital Pharmacists recently called for improved national information, vigilance and monitoring systems in relation to shortages, and the sharing of information and best practices on the management of shortages among relevant national regulatory bodies. It calls for the European heads of Medicines Agencies to jointly consider what new European-wide actions can assist the shortage problem, and develop a strategic joint position on medicines shortages. The EAHP calls for the European Medicines Agency to be involved in the pan-European solution-finding process.[5] The Pharmaceutical Group of the European Union has also raised the issue of shortages and calls for concrete action from governments, EU Institutions and supply chain partners.[6]

In addition to measures to maintain the availability of medicines, measures aimed at improving the timely communication of shortages to stakeholders are an important part in minimising the potential impact of shortages. Consistent communication to key stakeholders and the general public will help to maintain and improve trust in the regulatory system. Communication measures should include consistent, proportionate and timely website postings with helpful information for healthcare professionals and patients regarding the reasons for shortages and timelines for resolution[7].

## 2. Problem statement

This paper proposes changes to current communication practices for medicines evaluated by the European Medicines Agency (EMA). This document follows and complements the reflection paper on "medicinal product supply shortages caused by manufacturing/GMP compliance problems" (EMA/590745/2012) which summarises the lessons learned from previous shortage crises where the EMA had a supporting or co-ordinating role, and presents short and mid-term actions to allow the network to prevent, mitigate, and manage shortages of important medicinal products. These actions have been set out in an Implementation Plan 2012-2015 (EMA/708575/2012).They include the effective communication within the network, with international partners and with healthcare professionals, patients and the general public through the establishment of a public catalogue of current and past shortages of centrally authorised medicines with links to all relevant opinions and communications.

In addition, the current proposal also addresses the communication of any recalls of centrally authorised medicines. Recalls and shortages of medicines are often linked as a recall of a medicine may lead to its shortage. Public communication of recalls of medicines is also expected to improve transparency at the Agency.

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3 http://www.hematology.org/News/2012/8525.aspx

4 FIP calls attention to medicines shortages [Internet]. The Hague: International Pharmaceutical Federation; 2011. Available from: http://www.fip.org/www/index.php?page=latest_news&news=newsitem&newsitem=118

5 http://www.eahp.eu/sites/default/files/files/EAHPStatement%20on%20Medicines%20Shortages.pdf

6 http://www.pgeu.eu/en/press/1-press-releases/92-medicine-shortages-in-european-community-pharmacies.html

7 http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/meetings/twentyfourth/criticaldrugshortages.pdf

# 3. Lessons learned

Over the past two to three years the Agency has communicated on a number of recalls and short- and long-term supply shortages using question and answer documents and/or press releases. In the absence of a clear policy on communication in these circumstances, the decision to communicate has been made on a case by case basis. Communication was considered in cases where an assessment by the CHMP had been carried out together with the endorsement of a DHPC letter. Experience gained over the last three years shows that existing high profile communication tools are not optimal as they are not sufficiently flexible and do not address properly the varying supply situation and prescribing policies in Member States. In particular, the high visibility of press releases and/or a Q&A may if not well aligned with national communications be inappropriate and cause unnecessary alarm which could cause stock-piling exacerbating the supply situation in some Member States. In addition, press releases or Q&As are not always updated when the shortage is resolved and therefore remain on the website permanently providing potentially misleading or inaccurate information. Centralised information regarding shortages can often be condensed and does not warrant a press release or a detailed Q&A. Instead, the information provided should be kept high level and should allow for national differences (such as differences in the marketed formulations, differences in available alternatives,..). If relevant and available complementary and more detailed advice, tailored for each situation, can be provided at a national level.

To determine the most appropriate communication tools for the EMA, existing public information sources on shortages have been analysed.

In the USA, The Association of Health System Pharmacists and the Food and Drug Administration publish a weblisting of medicine shortages [8,9]. Both listings include information on current shortages and resolved shortages as well as other information for patients and consumers. The websites contain concise information on products affected by the shortage, the reason for the shortage, suitable alternatives and the expected resolution date. The information on the FDA website covers medically necessary as well as non-medically necessary medicines for which the FDA has received multiple requests for information. However it does not include information on shortages of brief duration or any shortages where the FDA is concerned that such information could make the shortage worse—for example, by provoking stock-piling. Once the shortage is resolved the information about the shortage is moved from the current shortages page to the resolved shortages page.[10]

In Europe, the level of information provided nationally varies and it is not readily available in all member states. Some national competent authorities currently publish a comprehensive Medicines shortage list on their website which includes expected dates of resolution and DHPC letters where available. A number of other national agencies publish selected DHPCs on their website or link to communication material published by the EMA for medicines in short supply.

# 4. Recommendations

In view of the lack of comprehensive information regarding shortages within the EU it is proposed that the EMA communicates more consistently using clearly defined criteria. It is proposed to use new and more flexible communication tools to ensure that the information is up-to-date and readily accessible.

[8] http://www.ashp.org/menu/DrugShortages/CurrentShortages.aspx
[9] http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm
[10] United States Government Accountability Office- Drug Shortages - FDA's ability to respond should be strengthened http://www.gao.gov/assets/590/587000.pdf

This will ensure timely, comprehensive, more transparent and more accessible communication on medicine shortages within the EU Network, with international partners and with healthcare professionals, patients and the general public which forms an important part in the management of medicine shortages. More transparent communication on medicines shortages allowing for complete, accurate and consistent provision of information can mitigate the impacts of shortages by allowing early planning. However, communication should be targeted, purposeful and of appropriate visibility to minimise the potential for panic buying or hoarding behaviour. Information at European level cannot be exhaustive in covering all medicine shortages occurring at national level. In terms of recommendations, any information provided at European level will only cover recommendations that have been agreed at CHMP level for shortages that affect more than one member state. It is recognised that the requirement for central communication needs to be balanced against the needs for tailored national communications. Any communication will also have to remain high-level to allow for possible national differences (differences in marketed formulations, differences in available alternatives,..) and should be complemented with more detailed communication at national level. Therefore changes to the way DHPCs on shortages are prepared at EU level are proposed. A 'core' DHPC should be agreed by the CHMP which can be used and adapted at national level according to the specific circumstances. Coordination within the EU Network also needs to be improved to ensure that communication is complementary. In this respect the timing of communication is particularly important when deciding to issue central communication and EMA will take the timing of national supply communication into account and try to align its communication.

## *4.1 Proposed actions*

Establish a public catalogue of medicines evaluated by the EMA that have experienced a shortage

It is proposed that EMA publishes information on potential, ongoing and resolved shortages of medicines that are centrally authorised or that are being evaluated as part of a community procedure (irrespective of whether the shortage is secondary to a recall, manufacturing capacity issue or discontinuation of a medicine) through a table on a dedicated webpage (which will itself not be presented as high profile or "news").

The EMA will only communicate via the mentioned catalogue when all of the following criteria apply:

- the shortage affects or is likely to affect more than one EU member state;
- an assessment by the PRAC and CHMP/CMDh has been carried out with recommendations to healthcare professionals (via a core DHPC) including a need for healthcare professionals to review patients' treatment.

The information provided in the catalogue will be based on the core DHPC agreed by CHMP or CMDh and will be sufficiently high level as to be applicable to all member states affected.

The information on a shortage will be published once nationally tailored DHPCs have been sent out in at least one but preferably more than one Member State taking into account the timing of national communications in countries that are most affected by the supply problem. EMA will engage in dialogue with patients' and consumers' organisations (PCOs) and healthcare professionals' organisations to ensure they receive timely information on shortages which may be relevant for them.

The catalogue will be updated to clearly reflect the current status of a shortage (potential, ongoing or resolved). It will be the responsibility of the company to provide information on the shortage situation to the PTL who will ensure that the information on the website is updated.

The public catalogue will replace the need for high-profile communication (press release or Q&A in most cases). Only in the following specific circumstances will the EMA continue to issue a high-profile press releases and/or a Q&A document:

- in cases where the shortage is linked to clear evidence of a safety concern in the context of a safety referral evaluated by the Agency.
- in cases where it is anticipated that the shortage could have serious public health implications across the EU

In all cases, communication will acknowledge that national supply situations may vary, and that complementary/additional national communications/advice may be issued.

The following table is proposed (see annex for mock-up):

| | **Medicine (INN)**<br>**Strength(s) and formulation(s)** |
|---|---|
| **Indication** | |
| **Reason for shortage** | < Information issued previously by the EMA on the supply situation for X can be found here> |
| **Member States affected*** <br><br>* This information is accurate at time of last update and may change. For accurate information about the status of a medicine shortage in a particular member state the national competent authority should be contacted. | |
| **Information to HCPs ( based on core DHPC)** | *High level (to allow for differences in Member States)*<br><br>*As appropriate include the following statement: 'additional advice may be available from the national competent authority'* |
| **Information to patients (based on core DHPC)**. | *As above* |
| **Status (potential/ongoing/ resolved)** | *Include information on duration of shortage or expected date of resolution if available* |
| **Date of last update** | **Optional** |

It is hoped that by using the above criteria and by providing the information in this format, information will be consistent, more up-to-date and accessible.

The information provided will not cover all shortages of medicines in Europe as it only relates to shortages affecting more than one MS and where DHPCs with a core EU message have been approved by the CHMP and issued (in accordance with national tailoring). This means that the information provided by the EMA on shortages does not provide a complete picture of the medicine supply situation in Europe and should be seen as complementary to any information provided at national level. The website will clearly state the criteria for inclusion in the table and the fact that not all shortages are

listed. In addition it will also clearly state that the impact of a shortage may vary depending on the country and that for additional information the national competent authorities should be contacted.

The catalogue format has the advantage of a lower profile while being more user friendly than the current approach of published Q&A documents (easier to find and search). This may be desirable in cases where there is a potential for panic buying or stock-piling behaviour.

Establish a public catalogue of Centrally Authorised Products (CAPs) that have experienced a recall

As recalls and shortages of medicines are often linked and a recall of a medicine may lead to its shortage, it is proposed that the EMA publishes information on class I, II & III recalls of centrally authorised medicines. In addition, the public communication of recalls of medicines is of interest to the public and would increase the transparency of the Agency. This would help to increase trust in the regulatory system.

A webpage similar to the one for shortages is proposed for listing class I, II & III recalls and any communication material that may be issued.

The following table is proposed:

| | **Medicine (INN)**<br>**Strength(s) and formulation(s)** |
|---|---|
| **Indication** | |
| **Type of recall (type I / type II / Type III)** | |
| **Presentation, number and expiry date and number of batch(es) affected** | |
| **Member States affected** | |
| **Reason and date of recall** | |
| **Information to HCPs (based on core DHPC if available)** | *High level (to allow for differences in Member States)*<br><br>*As appropriate include the following statement: 'additional advice may be available from the national competent authority'* |
| **Information to patients (based on core DHPC if available)** | *As above* |
| **Other relevant EMA communication where available (PR / Q&A)** | **Optional** |
| **Did the recall result in a shortage** | |

Specific information to healthcare professionals and patients will be issued if an assessment by the PRAC/CHMP has been carried out with recommendations to healthcare professionals (via DHPC).

As for shortages, for some recall situations, the issuing of a press release and/or a Questions and answer document will be considered in cases where the recall is linked to clear evidence of a safety concern in the context of a safety referral being evaluated by the Agency and in cases where it is anticipated that the recall could have serious public health implications across the EU.

Streamline the preparation and review of DHPCs on shortages by CHMP

Based on experience over the past years, there have often been difficulties when a single EU DHPC has not allowed for sufficient tailoring of national messages. The different shortage situations in the different Member States offer the potential for complex scenarios which one single message cannot properly address; in some situations the CHMP has agreed two DHPCs in an attempt to cover national differences. This has not proven to be satisfactory.

Instead it is proposed that whenever the CHMP decides that a DHPC is needed to deal with a shortage, a document setting out core EU DHPC messages is agreed. These core EU messages can be complemented with optional paragraphs which can be chosen to make up the DHPC as per the different national situations (for example in relation to availability and choice of alternative treatments). This will allow for a 'core' DHPC to be used and adapted at national level according to the specific circumstances.

Although national tailoring of the DHPC will be permitted; tailoring should preserve any core messages which CHMP considers applicable in all Member States (i.e.tailoring should not conflict with these core messages).

Obtain specific feedback on use from PCOS and healthcare professional organisations

It is proposed to obtain feedback from PCOs and healthcare professional organisations on how the information is used. This could be supplemented with a web-based user survey linked to the Q&As on shortages and recalls on our website.

# 5. Annex I – Mock-up for catalogue of medicines (potentially) affected by shortage

| Depocyte (cytarabine)<br>suspension for inthecal injection | |
|---|---|
| **Indication** | DepoCyte is a medicine used to treat lymphomatous meningitis. |
| **Reason for shortage** | In August 2012, an inspection highlighted deficiencies in the manufacturing process of DepoCyte, relating to a lack of adequate sterility assurance. As a result of the inspection findings, Pacira Pharmaceuticals Inc put further production and release of DepoCyte on hold. Manufacture of new batches of DepoCyte was halted pending a resolution of the issues to be confirmed by a re-inspection of the facilities. As a precaution DepoCyte was recalled in European Union (EU) countries where suitable alternative treatments are available. |
| **Member States affected**[11] | All EU Member States where Depocyte was previously available. |
| **Information to HCPs** | • HCPs to receive a letter from MAH.<br>• Additional advice may be available from your national competent authority. |
| **Information to patients** | • Patients who are currently treated with DepoCyte may need to switch to alternative treatments.<br>• Patients who have any questions should speak to their doctor or pharmacist.<br>• Additional advice may be available from your national competent authority. |
| **Status** | ongoing |

[11] This information may change. For accurate information about the status of a medicine shortage in a particular member state the national competent authority should be contacted.

| Increlex (mecasermin)<br>solution for subcutaneous injection | |
|---|---|
| **Indication** | Increlex is used for the long-term treatment of patients aged 2 to 18 years who are of short stature due to a condition known as 'severe primary insulin-like growth factor-1 deficiency'. |
| **Reason for shortage** | In April 2013, problems at the manufacturing site in the United States led to an interruption in the manufacture of the active substance. The problems were linked to equipment failures at the site which are currently being addressed by the company |
| **Member States affected**[2] | All European Union (EU) Member States where Increlex was previously available. |
| **Information to HCPs** | • Healthcare professionals to receive a letter from MAH. The letter contains detailed information on the shortage of Increlex in their country.<br>• No new patients should be started on Increlex until normal supplies are re-established.<br>• There are no alternative treatment options for severe primary insulin-like growth factor-1 deficiency. When stopping treatment, hypoglycaemia could recur in patients (especially young children) who experienced hypoglycaemic episodes before starting treatment with Increlex. Patients may therefore have to be monitored as appropriate.<br>• Additional advice may be available from your national competent authority. |
| **Information to patients** | • Patients will be informed of the upcoming shortage of Increlex by their treating physicians.<br>• There will be a period during which Increlex will be unavailable. During this period, you may have to be regularly reviewed by your doctor. Available evidence suggests that it is possible to stop and restart treatment with Increlex without significant concerns.<br>• Patients who have any questions should speak to their doctor or pharmacist.<br>• Additional advice may be available from your national competent authority. |
| **Status** | ongoing |

| Fabrazyme (agalsidase beta)<br>solution for infusion | |
|---|---|
| **Indication** | Fabrazyme is used to treat patients who have Fabry disease. |
| **Reason for shortage** | The supply shortage of Fabrazyme began in June 2009 and was caused by a series of manufacturing problems at one of the manufacturing sites. Information issued previously by the EMA on the supply situation for Fabrazyme can be found here. |
| **Member States affected**[12] | All European Union (EU) Member States where Fabrazyme was previously available. |
| **Information to healthcare professionals** | • Stock levels are improving, however the product supply remains vulnerable to disruption.<br>• With the current stock levels, patients currently treated with Cerezyme can receive a full dose, as recommended in the summary of product characteristics.<br>• Healthcare professionals who wish to start new patients should contact the company. New patients can be started as long as existing stocks are sufficient to allow for continued treatment.<br>• Additional advice may be available from your national competent authority. |
| **Information to patients** | • Stock levels are improving, however the product supply remains vulnerable to disruption.<br>• If you are currently treated with Cerezyme, your doctor will now be able to prescribe you a full dose.<br>• New patients may now be able to receive Cerezyme.<br>• Patients who have any questions should speak to their doctor or pharmacist.<br>• Additional advice may be available from Eurordis, an organisation representing people with rare diseases in Europe or EGA (European Gaucher Alliance). Alternatively advice may be available from your national competent authority. |
| **Status** | Ongoing |

[12] This information may change. For accurate information about the status of a medicine shortage in a particular Member State the national competent authority should be contacted.

| Cerezyme (imiglucerase)<br>solution for infusion | |
|---|---|
| **Indication** | Cerezyme is used for the long-term treatment of patients with Gaucher disease. |
| **Reason for shortage** | The supply shortage of Cerezyme began in June 2009 and was caused by a series of manufacturing problems at one of the manufacturing sites. Information issued by the EMA previously on the supply situation for Cerezyme can be found here. |
| **Member States affected**[13] | All European Union (EU) Member States where Cerezyme was previously available. |
| **Information to healthcare professionals** | • Stock levels are improving, however the product supply remains vulnerable to disruption.<br>• With the current stock levels, patients currently treated with Cerezyme can receive a full dose, as recommended in the summary of product characteristics.<br>• Healthcare professionals who wish to start new patients should contact the company. New patients can be started as long as existing stocks are sufficient to allow for continued treatment.<br>• Additional advice may be available from your national competent authority. |
| **Information to patients** | • Stock levels are improving, however the product supply remains vulnerable to disruption.<br>• If you are currently treated with Cerezyme, your doctor will now be able to prescribe you a full dose.<br>• New patients may now be able to receive Cerezyme.<br>• Patients who have any questions should speak to their doctor or pharmacist.<br>• Additional advice may be available from Eurordis, an organisation representing people with rare diseases in Europe or EGA (European Gaucher Alliance). Alternatively advice may be available from your national competent authority. |
| **Status** | Ongoing |

[13] This information may change. For accurate information about the status of a medicine shortage in a particular Member State the national competent authority should be contacted.

# 6. Annex II - proposed text for website and catalogue listing - September 2013

## Medicine shortages

**This page contains information on medicine shortages that have been assessed by the European Medicines Agency.**

In the European Union, the distribution of medicines in each Member State is primarily the responsibility of the national competent authority. Most medicine shortages are therefore dealt with at national level.

However, the European Medicines Agency can be involved in certain situations, for example when a medicine shortage is linked to a safety concern or affects several Member States.

Medicine shortages can occur for many reasons, such as manufacturing difficulties or problems affecting the quality of medicines that can impact on patient care. Regulatory authorities within and outside Europe are increasingly working together to prevent shortages and to limit their impact whenever they occur.

European regulatory authorities aim to minimise the impact of medicine shortages on patients by:

- working with pharmaceutical companies to resolve manufacturing and distribution issues;
- sharing information with international partners about alternative sources of supply;
- seeking input from patients and healthcare professionals on the impact of medicine shortages, to support decision-making;
- taking measures to allow alternative medicines or suppliers to be used.

The Agency maintains a list of medicine shortages that it has assessed.

## List of medicine shortages

**This page lists the medicine shortages that have been assessed by the European Medicines Agency.**

The list contains information on shortages that affect or are likely to affect more than one European Union Member State, where the Agency has assessed the shortage and provided recommendations to patients and healthcare professionals across the EU.

It does not give a complete overview of all medicine shortages occurring in the EU, as most shortages are dealt with at a national level.

For each shortage listed below, additional information about the situation in a specific country may be available from the national competent authority.

There may be medicines in short supply that are not listed here. If you cannot find information on a medicine in short supply or you would like further information, please visit the website of your national competent authority.

If you are having difficulty obtaining a medicine that has been prescribed to you, talk to your doctor or pharmacist.

**Current shortages**

[Document listing of PDFs describing current shortages]

**Resolved shortages**

[Document listing of PDFs describing resolved shortages – moved down from list above as necessary]

# Recalls of medicines

**This page provides information on the removal of medicines from the market in the European Union. This may be necessary because it is found to be defective or potentially harmful. This is called a 'recall' and is done in order to protect public and animal health.**

When a recall is necessary, regulatory authorities issue alerts to healthcare professionals and wholesalers to inform them about the recall. These alerts are graded according to the seriousness of the threat:

- **Class 1** requires immediate recall because the product poses a serious or life-threatening risk to health.
- **Class 2** specifies a recall within 48 hours because the defect could harm the patient but is not life-threatening.
- **Class 3** requires action to be taken within five days because the defect is unlikely to harm patients and is being carried out for reasons other than patient safety.

Most recalls fall into classes 2 or 3.

The European Medicines Agency evaluates all quality concerns for medicines it assesses via the centralised procedure. It coordinates recalls of medicines if their safety or effectiveness is compromised.
Information on recalls of medicines initiated by the Agency is available in the list below.
The Agency only initiates recalls of medicines that are centrally authorised, so the list below does not give a complete overview of all recalls in the European Union. Some EU recalls are not listed in this catalogue.
If you cannot find the necessary information on a recalled medicine, visit the website of your national competent authority.
[Document listing of PDFs describing recalls]