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SCIENCE MEDICINES HEALTH

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Patient Health Protection

## Communication by the European Medicines Agency on supply shortages of medicinal products

Discussed by CHMP	June 2013
Adopted by CHMP	September 2013

### 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. Shortages have affected all classes of medicines including 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 vary widely 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 setting-up of patient allocation programs (as was the case for Myzozyme, Cerezyme and Fabrazyme). They can have detrimental effects on patient care as they can lead to medicines rationing, delay of critical treatments, and cause patients to use 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 to suboptimal treatment outcomes.

The seriousness of shortages that have occurred 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 reporting on shortages by the U.S. Food and Drug Administration (FDA) to the US Congress, the establishment of a medicines 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.<sup>1</sup> 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 shortages by publicly conveying the seriousness of the crisis and proposing potential solutions. 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.<sup>2</sup> 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 medicines supply so that appropriate treatment for patients can be initiated and maintained.<sup>3</sup>

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 in dealing with the shortage problem and to develop a strategic joint position on medicines shortages. The EAHP calls for the European Medicines Agency (EMA) to be involved in the pan-European solution-finding process<sup>4</sup>. 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.<sup>5</sup>

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 their potential impact. 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.<sup>6</sup>

## 2. Problem statement

This paper addresses changes to current communication practices for medicines evaluated by the European Medicines Agency (EMA). It 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 communication material.

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<sup>1</sup><http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCA/SignificantAmendments/totheFDCA/FDASIA/ucm313121.htm>

<sup>2</sup><http://www.hematology.org/News/2012/8525.aspx>

<sup>3</sup> 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](http://www.fip.org/www/index.php?page=latest_news&news=newsitem&newsitem=118)

<sup>4</sup><http://www.eahp.eu/sites/default/files/files/EAHPStatement%20on%20Medicines%20Shortages.pdf>

<sup>5</sup><http://www.pgeu.eu/en/press/1-press-releases/92-medicine-shortages-in-european-community-pharmacies.html>

<sup>6</sup><http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/meetings/twentyfourth/criticaldrugshortages.pdf>

### 3. Lessons learned

Over the past two to three years the EMA has communicated on a number of short- and long-term supply shortages using question and answer documents (Q&As) 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 the CHMP has conducted an assessment and endorsed a Direct Health Professional Communication (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 different supply situations and prescribing policies in Member States. In particular, the high visibility of press releases and/or Q&As 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. 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 and in available alternatives). Complementary and more detailed advice, tailored for each situation, can then 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 web listing of medicine shortages.<sup>7,8</sup> Both listings include information on current 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' medicines as well as those considered non-medically necessary for which the FDA has received multiple requests for information. However it does not include information on shortages of brief duration. Once the shortage is resolved the information about the shortage is moved to a separate page for resolved shortages.<sup>9</sup>

In the EU, 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 should communicate more consistently using clearly defined criteria. It is proposed that new and more flexible communication tools be used to ensure that the information is up-to-date and readily accessible. 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

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<sup>7</sup> <http://www.ashp.org/menu/DrugShortages/CurrentShortages.aspx>

<sup>8</sup> <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>

<sup>9</sup> United States Government Accountability Office- Drug Shortages - FDA's ability to respond should be strengthened <http://www.gao.gov/assets/590/587000.pdf>

by allowing early planning. However, communication should be targeted, purposeful and drafted in such a way as to minimise the potential for panic buying or hoarding behaviour. Information at European level cannot cover 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 communication. Any communication will also have to remain high-level to allow for possible national differences (such as differences in marketed formulations and 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 manufacturing capacity issue or discontinuation of a medicine) through a table on a dedicated webpage.

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 EMA 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):

<b>Medicine (INN) Strength(s) and formulation(s)</b>	
<b>Indication</b>	
<b>Reason for shortage</b>	< Information issued previously by the EMA on the supply situation for X can be found here >
<b>Member States affected*</b>	
* 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.	
<b>Information to HCPs ( based on core DHPC)</b>	<i>High level (to allow for differences in Member States) As appropriate include the following statement: 'additional advice may be available from the national competent authority'</i>
<b>Information to patients (based on core DHPC).</b>	<i>As above</i>
<b>Status (potential/ongoing/ resolved)</b>	<i>Include information on duration of shortage or expected date of resolution if available</i>
<b>Date of last update</b>	<b>Optional</b>

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.

[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 too 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 there will be national tailoring of DHPCs, any core messages which CHMP considers applicable in all Member States should be preserved (i.e. tailoring should not conflict with these core messages).

#### Obtain specific feedback on use from PCOS and healthcare professional organisations

It is proposed that the EMA obtains feedback from patients and consumer organisations 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

<b>Increlex (mecasermin) solution for subcutaneous injection</b>	
<b>Indication</b>	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'.
<b>Reason for shortage</b>	<p>In April 2013, problems at the manufacturing site in the United States led to an interruption in the manufacture of the active substance. This led to a shortage in the supply of Increlex in August 2013. The problems were linked to equipment failures at the site which are currently being addressed by the company.</p> <p>Information issued previously by the EMA on the supply situation for Increlex can be found <a href="#">here</a>.</p>
<b>Member States affected<sup>10</sup></b>	All European Union (EU) Member States where Increlex was available.
<b>Information to HCPs</b>	<ul style="list-style-type: none"> <li>• A letter from the marketing authorisation holder was sent out to healthcare professionals in April 2013.</li> <li>• No new patients should be started on Increlex until normal supplies are re-established.</li> <li>• There are no alternative treatment options for severe primary insulin-like growth factor-1 deficiency and patient's treatment will have to be interrupted. When stopping treatment hypoglycaemia could re-occur in patients who experienced hypoglycaemic episodes before starting treatment with Increlex. Patients should therefore be monitored as appropriate.</li> <li>• The marketing authorisation holder has established an advisory board of external experts to answer any queries from healthcare professionals. Contact details are included in the letter that was sent to healthcare professionals or are available from the company.</li> <li>• Additional advice may be available from the <a href="#">national competent authority</a>.</li> </ul>
<b>Information to patients</b>	<ul style="list-style-type: none"> <li>• Increlex is currently unavailable and treatment will have to be interrupted. During this period, patients may have to be regularly</li> </ul>

<sup>10</sup> 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) solution for subcutaneous injection

	<p>reviewed by their doctor.</p> <ul style="list-style-type: none"><li>• There are no alternative treatment options for severe primary insulin-like growth factor-1 deficiency.</li><li>• Patients who have any questions should speak to their doctor or pharmacist.</li><li>• Additional advice may be available from the <a href="#">national competent authority</a>.</li><li>• Patients may also contact <a href="#">Eurordis</a>, an organisation representing people with rare disease in Europe.</li></ul>
<b>Status</b>	Ongoing
<b>Date of publication</b>	4 November 2013



## Fabrazyme (agalsidase beta) solution for infusion

<b>Indication</b>	Fabrazyme is used to treat patients who have Fabry disease.
<b>Reason for shortage</b>	The supply shortage of Fabrazyme began in June 2009 and was caused by a series of manufacturing problems at one of its manufacturing sites. Information issued previously by the EMA on the supply situation for Fabrazyme can be found <a href="#">here</a> .
<b>Member States affected<sup>11</sup></b>	All European Union (EU) Member States.
<b>Information to healthcare professionals</b>	<ul style="list-style-type: none"> <li>• Stock levels are continuing to improve, however the product supply remains vulnerable to disruption.</li> <li>• Based on current stock levels, patients currently treated with Fabrazyme can receive the full dose recommended in the summary of product characteristics.</li> <li>• Healthcare professionals who wish to start new patients should contact the company prior to starting treatment. New patients can be started as long as existing stocks are sufficient.</li> <li>• Additional advice may be available from the <a href="#">national competent authority</a>.</li> </ul>
<b>Information to patients</b>	<ul style="list-style-type: none"> <li>• Stock levels are continuing to improve, however the product supply remains vulnerable to disruption.</li> <li>• For patients who are currently being treated with Fabrazyme, the treating doctor will now be able to prescribe the full dose.</li> <li>• New patients may now be able to receive Fabrazyme.</li> <li>• Patients who have any questions should speak to their doctor or pharmacist.</li> <li>• Additional advice may be available from the <a href="#">national competent authority</a>.</li> <li>• Patients may also contact <a href="#">Eurordis</a>, an organisation representing people with rare diseases in Europe, or <a href="#">Fabry International Network</a> (FIN).</li> </ul>
<b>Status</b>	Ongoing
<b>Date of publication</b>	4 November 2013

<sup>11</sup> 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) solution for infusion

<b>Indication</b>	Cerezyme is used for the long-term treatment of patients with Gaucher disease.
<b>Reason for shortage</b>	The supply shortage of Cerezyme began in June 2009 and was caused by a series of manufacturing problems at one of its manufacturing sites. Information issued by the EMA previously on the supply situation for Cerezyme can be found <a href="#">here</a> .
<b>Member States affected<sup>12</sup></b>	All European Union (EU) Member States.
<b>Information to healthcare professionals</b>	<ul style="list-style-type: none"> <li>• Stock levels are continuing to improve, however the product supply remains vulnerable to disruption.</li> <li>• Based on current stock levels, patients currently treated with Cerezyme can receive the full dose recommended in the summary of product characteristics.</li> <li>• Healthcare professionals who wish to start new patients should contact the company prior to starting treatment. New patients can be started as long as existing stocks are sufficient.</li> <li>• Additional advice may be available from the <a href="#">national competent authority</a>.</li> </ul>
<b>Information to patients</b>	<ul style="list-style-type: none"> <li>• Stock levels are continuing to improve, however the product supply remains vulnerable to disruption.</li> <li>• For patients who are currently being treated with Cerezyme, the treating doctor will now be able to prescribe the full dose.</li> <li>• New patients may now be able to receive Cerezyme.</li> <li>• Patients who have any questions should speak to their doctor or pharmacist.</li> <li>• Additional advice may be available from the <a href="#">national competent authority</a>.</li> <li>• Patients may also contact <a href="#">Eurordis</a>, an organisation representing people with rare diseases in Europe.</li> </ul>
<b>Status</b>	Ongoing
<b>Date of publication</b>	4 November 2013

<sup>12</sup> 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, most medicine shortages are dealt with at national level by the national competent authorities.

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 catalogue of shortages that it has assessed.

### List of medicine shortages

**The shortages catalogue contains information on medicine shortages that affect or are likely to affect more than one European Union (EU) Member State, where the European Medicines 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.