Access to Medicines Before Market Authorisation or Marketing

Guidelines

These guidelines are intended to broadly explain the available methods to provide patients with access to medicines before they are marketed or receive marketing authorization (are registered). Emphasis will be placed on early access to new medicines without marketing authorization through programmes known as Early Access Programmes or Managed Access Programmes. These include two types of pathways: Compassionate Use (CU) and Named Patient Programmes (NPP). It is important to distinguish between the two.

General rule – registered and marketed medicines

Most medicines sold in pharmacies in Iceland have marketing authorization from the Icelandic Medicines Agency (IMA) and are available in the country because their marketing authorization holder (MAH) has decided to market them in Iceland. Marketing authorization from the IMA (registration of a medicine) is a prerequisite for marketing, which involves listing the medicine in the medicinal products register and the Icelandic Medicine Price Catalogue (IMPC).

The Icelandic Medicine Price Catalogue (IMPC) contains medicines that have received approved maximum wholesale prices (MWP) from the IMA. These medicines are either not marketed, known as exempt medicines, with approved MWP, or medicines that are marketed and have approved MWP. The IMPC is the bases for prescription system called Saga, owned by the Directorate of Health.

Icelandic Medicinal Product Information Database (IMPID, www.serlyfjaskra.is) includes medicines that have marketing authorization and are marketed; no information on exempt medicines is found in the medicinal products register.

Other methods – special circumstances

The general rule is that marketing authorization from the IMA is the basis for selling medicines in Iceland, as stated in Article 11 of the Medicines Act: "*Only medicines that have been granted marketing authorization by the Medicines Agency may be marketed in this country*." There are, however, some exceptions that may grant patients access to medicines and allow doctors to prescribe medicines that do not have marketing authorization and/or are not marketed. Access to medicines before they are marketed or receive marketing authorization can broadly be obtained through three methods: clinical trials, a doctor's authorization to prescribe exempt medicines, and through programmes by the MAH.

1. Clinical trials

About clinical trials – A clinical drug trial is a systematic study of a medicine to obtain knowledge or confirm knowledge about its effect, interactions, side effects, pharmacokinetics, or to investigate its therapeutic value. In most cases, the medicine does not have marketing authorization, but studies are also conducted on new uses of medicines that have marketing authorization and are marketed.

Legal basis – Regulation on clinical trials of medicinal products for human use no. 1311/2021, established pursuant to Article 22 of the Medicines Act no. 100/2020 and Article 34 of the Act no. 44/2014 on scientific research in the field of health. **Prescribing by doctors** – Medicines investigated in clinical trials are not prescribed through the prescription system used by doctors, such as the SAGA system, which is based on the price list or the medicines database of the Directorate of Health. **Further information** – More information on clinical trials can be found on the Medicines Agency's website, here.

2. Exempt Medicines with Approved Maximum Wholesale Price

About Exempt Medicines - This section deals with exempt medicines that have received approval for a maximum wholesale price (MHWP) from the Icelandic Medicines Agency and are listed in the Icelandic Medicine Price Catalogue (IMPC). Exempt medicines are not marketed, and information about them cannot be found in the Icelandic Medicinal Product Information Database (IMPID). Exempt medicines do not have to meet all the same requirements as marketed medicines. For example, information on the inner and outer packaging may not be in Icelandic, the marketing authorisation holder is not legally required to notify about drug shortages, and there is no need to meet conditions regarding educational materials, etc. Reasons for prescribing an exempt medicine include instances when there is a shortage of a marketed medicine (i.e., the medicine is not available) or when no medicine is marketed for specific diseases. Exempt medicines can be roughly divided into two categories depending on whether a marketing authorisation exists or not:

- **The exempt medicine has a marketing authorisation (registered) in Iceland or in the European Economic Area but is not marketed** - It is the decision of the marketing authorisation holder whether the medicine is marketed in the country or not. In these cases, the text on the packaging and the leaflet is not in Icelandic. Therefore, it is necessary to ensure that patients receive the required information. The treating doctor is responsible, among other things, for informing the patient about possible side effects and other necessary information for the use of the medicine.

- **The exempt medicine does not have a marketing authorisation (unregistered) in Iceland or in another country within the European Economic Area** - If the medicine does not have a marketing authorisation in the European Economic Area, which is rare, the doctor bears full responsibility for prescribing and the effectiveness of the medicine in question, according to Article 12 of the Medicines Act No. 100/2020, here.

  Here is a list of medicines with marketing authorisation in the European Economic Area.

Legal Basis - The doctor's authority to prescribe a medicine without a marketing authorisation is the same as for prescribing exempt medicines. Refer to paragraphs 2 and 3 of Article 11 of the Medicines Act No. 100/2020 and exempt medicines according to Article 12 of the Medicines Act No. 100/2020.

Doctors' Prescriptions - A doctor can prescribe exempt medicines that have been approved with a maximum wholesale price by the Icelandic Medicines Agency and are listed in the pharmaceutical price list, in two ways. Firstly, through the prescription system, such as the Saga system, or through the Pharmaceutical Database of the Directorate of Health. All inquiries regarding the database and the Saga system should be directed to the Directorate of Health, which operates these systems.

The Medicines Agency does not have the authority to approve an exempt prescription if a similar marketed medicine is available in the pharmaceutical price list, unless the marketed medicine is in short supply or the doctor provides reasons why the marketed medicine cannot be used.

Further Reading - More detailed information about exempt medicines can be found on the LST website, here.

3. **Early access to a new medicine without marketing authorization through programmes (Early Access Programmes or Managed Access Programmes)**
Many terms exist in English and Icelandic to describe the process of providing patients with access to medicines without marketing authorization through defined programmes. Examples of such terms include Compassionate Use programme, Early Access Programme, Named Patient Programme, Managed Access Programme, Pre-Licence Patient Use, and sometimes these are confused with off-label use. It is important to define and clarify terms to enhance transparency and clarity. The fact is that these terms are not standardized across the countries of the European Economic Area, which causes confusion; for example, the same term might be used to describe different things. Regardless of this terminological confusion, these programmes have in common that they provide early access to new medicines before the medicine receives marketing authorization, i.e., is registered. The following aims to define these terms in accordance with the definitions of the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA).

   Early Access Programmes are divided into two categories: Compassionate Use (CU) and Named Patient Programmes (NPP). The authorization and responsibility of doctors for prescribing medicines under these programmes are based on different legal and regulatory frameworks. Therefore, it is very important to distinguish between these two categories.

   Compassionate Use (CU).

   The Medicines Agency has the authority to grant permission to offer a medicine for compassionate use. Medicines used for compassionate use do not have marketing authorization in the European Economic Area. Compassionate Use involves making a particular medicine available for compassionate use to a group of patients with a disease that causes long-term or serious disability, or a disease considered life-threatening, and which cannot be treated satisfactorily with a medicine that has marketing authorization in the European Economic Area. An application for a centralized marketing authorization (Centralized procedure, CP) for the medicine must be pending, or clinical trials for it must have been authorized. Article 11 of the Medicines Act states that only medicines that have been granted marketing authorization by the Medicines Agency may be marketed in this country. Despite this provision, the use of a limited quantity of medicinal products that have not been granted marketing authorization in this country is permitted for compassionate reasons, in accordance with a regulation issued by the Minister on conditions for granting permission for the use of medicines for compassionate reasons, according to Article 13 of the Medicines Act. This provision is part of the implementation of the European Parliament and Council regulation no. 726/2004. Regulation no. 424/2023 on the use of medicinal products for compassionate reasons came into force in April 2023.

The following conditions must be met to grant permission to offer a medicine for compassionate use:

a. An application for a centralized marketing authorization for the medicine is pending with the European Medicines Agency but has not been processed, or the medicine is the subject of a clinical trial and it is evident that the relevant patient group cannot participate in that trial.

b. The medicine is intended for a group of patients with a disease that causes long-term or serious disability, or a disease considered life-threatening.

c. The disease cannot be treated satisfactorily with a medicine that has marketing authorization in the European Economic Area.

d. Sufficient evidence must exist that the risk-benefit ratio of the medicine is considered to be largely positive for the relevant patient group.

The Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) published a comprehensive guide on the conditions that must be met when offering a medicine for compassionate use, see here.

a. HMA- Compassionate use program (hma.eu)**,** Timely Access group 2018_09_CUP_27-6-18.pdf (hma.eu)

b. EMA Compassionate use | European Medicines Agency (europa.eu). Questions and Answers, here. Guidelines, here.

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Icelandic Medicines Agency

Named Patient Programmes (NPP).

The Named Patient Program (NPP) is based on a doctor's authority to use medicines without a marketing authorisation, the same authority that applies to prescribing exempt medicines. A doctor's authority to prescribe exempt medicines is based on Article 12 of the Medicines Act, referring to Article 5(1) of Directive 2001/83/EC of the European Parliament and Council.

It is important to note that the prescription of exempt medicines without a marketing authorisation through the NPP, which are sometimes provided at no cost to the public and patients, differs from the prescription of exempt medicines listed in the pharmaceutical price list and with an approved maximum wholesale price (MHWP). If the Icelandic Medicines Agency (Lyfjastofnun) provides an exempt medicine through the NPP at no cost, the medicine is prescribed through "My Pages" on the Lyfjastofnun website. The doctor prescribes the medicine to an individual, as suggested by the name of the program, i.e., Named Patient Program (NPP). However, this does not mean that only one patient can be prescribed the medicine.

There is no need to apply for permission from Lyfjastofnun for the NPP, as the doctor already has the authority to prescribe medicines without a marketing authorisation, i.e., exempt medicines. However, it is crucial to consider, before starting treatment, how to prevent treatment disruption when a company decides to close a program; see more in the table below, FAQs.

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Icelandic Medicines Agency

Questions and Answers about the Difference between Compassionate Use and Named Patient Programs

	Compassionate Use (CU) **(Cohort)**	**Named Patient Programmes (NPP)**
Legal basis	Regarding permission for the use of medicinal products on compassionate grounds, it is addressed in Article 13 of the Medicinal Products Act, which concerns the authorization for the use of a limited quantity of human medicines that have not been granted marketing authorisation in this country. This provision implements Article 83 of the Regulation (EC) No 726/2004 of the European Parliament and of the Council. The provision is further elaborated in the Regulation on the use of medicinal products on compassionate grounds No. 424/2023.	The authorization granted to a physician to use drugs without marketing authorization is the same authorization as that for the use of exemption drugs, as referred to in paragraphs 2 and 3 of Article 11 of the Medicines Act No. 100/2020 and exemption drugs referred to in Article 12 of the Medicines Act No. 100/2020. See also the subsection "Comparison to individual basis treatment" on the EMA (European Medicines Agency) website.
Status of product	An application for a centralised marketing authorisation for the drug (Central Procedure, CP) is pending with the European Medicines Agency but has not yet been approved, or the drug is the subject of a clinical trial, and it is established that the relevant patient group cannot participate in that trial.	Decision of the company (MLH/Agent)

Who applies for authorisation for the programme to the Medicines Agency?	The company (MLH or representative) applies for it. The applicant is also the entity that has applied for a central marketing authorisation for the medicine or the manufacturer of the medicine being tested in a clinical trial, and is applying for permission to offer the medicine for compassionate use. In this country, applications are made to the Medicines Agency. The application form can be found on the Medicines Agency's website under published material → forms. The required documents are listed on the application form.	There is no need to apply for permission for an NPP to the Medicines Agency. The treating physician communicates with the company (marketing authorisation holder or representative) to gain access to the medicine through the NPP.
Decision and timelines	To assess the application, all conditions must be met, and all documents must have been submitted according to the application form. Payment must have been made according to the fee schedule. Once the opinion of the Committee for Medicinal Products for Human Use (CHMP) is available, the Medicines Agency shall process the application for permission to offer the medicine for compassionate use within 35 working days.	NA

Is approval from the EMA required for the programme?	Before the Medicines Agency grants permission to offer a medicine for compassionate use, an opinion from the CHMP must be available. This opinion is issued in consultation with the applicant and outlines the conditions for use and distribution, as well as the patients who should receive the medicine. See the list of Compassionate Use (CU) medicines that have received a CHMP opinion here. This list includes conditions for use, distribution, patient group definition, etc.	No
Does the Medicines Agency need to inform the EMA of its decision?	Yes	No
Is the Medicines Agency required to publish a list of programmes on its website?	Yes, according to regulations, it is mandatory. For comparison, you can find lists of programmes that have been approved in Sweden and Norway here: • Norway - Compassionate use program_ENG_2023-08-16.pdf (legemiddelverket.no) • Sweeden - Pågående godkända CUP | Läkemedelsverket (lakemedelsverket.se)	No The IMA can decide to do so.

Does the treating physician need permission from the healthcare institution where they work?	According to the regulations, the treating physician must seek approval from the medical director of the healthcare institution where they work before requesting access to a medicine from the applicant. Only the treating physician, on behalf of the patient, can request access to a medicine from the applicant, after the applicant has received permission from the Medicines Agency to offer the medicine for compassionate use	This is not addressed in the laws or regulations, but it is advisable that before treatment begins, the treating physician consult with the management of the healthcare institution where they work and together make a plan to prevent treatment interruption for the patient when the program ends.
What are the requirements for labelling of packaging and package leaflets while the program is open?	Information about the medicine, such as drafts of the summary of product characteristics, patient information leaflet, or labels, must be accessible.	The same requirements apply as for compassionate use medicines; see the question about the legal basis.
What documents are required?	The research protocol and information about the medicine, such as drafts of the summary of product characteristics, patient leaflet, or labelling, should be available.	The decision of the company (Marketing Authorisation Holder or Agent)

Programme begins – treatment can start		
Notification by the applican	According to the regulation, the applicant must annually send the Medicines Agency a list of the patient group using the drug, and updated information on the risk-benefit assessment. See more details in the regulation.	Does not apply; the Medicines Agency can request information from the company (marketing authorisation holder or Agent).
How is the medication prescribed in a programme while it is ongoing? **4o mini**	Treatment is not prescribed in the usual manner, such as through doctors' prescription systems, the Medicines Agency's My Pages, or the National Institute of Health's drug database. The dispensing of the medication is similar to what happens in clinical trials, i.e., in collaboration with the applicant (MLH or representative).	If the company provides the medication free of charge, an exemption drug authorization must be applied for a specific patient through the My Pages section on the Medicines Agency's website. If the company does not provide the medication at no cost, it must apply for the maximum wholesale price from the Medicines Agency. The medication will then be listed as an exemption drug in the drug price list and prescribed like other exemption drugs through the prescription system or the National Institute of Health's drug database.
What is the responsibility of the doctor?	The responsibility of the doctor is similar to that in clinical trials, as outlined in the regulations. Among other things, it is specified that the treating physician must inform the patient before starting the medication that continued treatment and state	The same responsibility as with the prescription of a compassionate use drug. The treating physician is responsible for informing the patient that the medication being prescribed does not have an Icelandic marketing authorisation, as well as explaining the potential

	coverage for the cost of the medication cannot be guaranteed after the program ends. The applicant (MLH or representative) must inform the treating physician without delay of any changes to the authorization to offer the medication for humanitarian use and any side effects of the medication. The treating physician must report any side effects experienced by the patient to both the Medicines Agency and the applicant.	side effects and any other information that may be necessary for the use of the medication. If the medication does not have marketing authorisation in any other European Economic Area (EEA) country, the doctor is entirely responsible for the prescription and the effects of the medication, according to the Medicines Act No. 100/2020, Section 12. Here is a list of drugs with marketing authorisation in the European Economic Area.
Hver greiðir fyrir kostnað lyfjameðferðar á meðan prógramm er í gangi, þ.e. á meðan enn er hægt er að taka inn nýja sjúklinga?	According to the regulations, the applicant (marketing authorisation holder or representative) must cover the costs until the programme ends, i.e., until no new patients can be enrolled in the programme.	Agreement between the treating physician, the healthcare institution they work for, and the company (marketing authorisation holder or representative).
	It is crucial, before the program begins, to ensure that there will be no interruption in treatment for patients, for example by making an agreement with the company (marketing authorisation holder or representative) regarding the continuation of treatment for those patients who have started it when the program ends. It cannot be assumed that the public sector will contribute to the cost of treatment without prior approval of payment coverage in one of the benchmark countries, and/or without an agreement on the price of the medicine, according to Regulation No. 1414/2020 on the pricing of medicines and payment contributions. It is beneficial for the treating physician to consult with the management of the healthcare institution they work for before initiating treatment, in order to reduce the risk of treatment interruption when the program ends. See below for answers to the question: "Who pays for the cost of medication after the program ends?	

End of Program – No New Patients Can Be Enrolled		
When does the programme end?	According to the regulations, the applicant must notify the Medicines Agency within 30 days if the drug has received marketing authorisation within the European Economic Area or if the clinical trial of the drug has been discontinued. The Medicines Agency can also terminate the programme. See Article 14 of Regulation No. 424/2023.	Ákvörðun fyrirtækis, í síðasta lagi The decision of the company, at the latest when the drug is marketed. After the drug is marketed, the Medicines Agency does not have the authority to approve compassionate use prescriptions according to Article 12 of the Medicines Act No. 100/2020.
What kind of registration process is behind the marketing authorisation?	Centralized procedure. The centralized procedure is used when applying for a marketing authorisation for the entire EEA area, for example, for biotechnology medicines, medicines for specific diseases, and other new medicines. Applications are submitted to the European Medicines Agency (EMA). The Committee for Medicinal Products for Human Use (CHMP) at EMA is responsible for evaluating the applications.	The decision of the company (Marketing Authorisation Holder or Agent)
Who pays for the cost of continued drug treatment after the programme ends and how is the treatment prescribed?	When a company (MLH or representative) decides to terminate a programme, i.e., decides that no new patients can be started on treatment, the question arises about who will cover the cost of continued treatment. It is crucial, before the programme begins, to try to ensure that there will be no treatment interruption for patients.	

	The company can choose to provide continued treatment at no cost to patients who are already in the programme when it ends. In this case, treatment continues to be prescribed in the same manner, i.e., the treating physician applies for permission to use an exemption drug for a specific patient through the "Mínar síður" section on the website of the Icelandic Medicines Agency. For instance, the company might decide to provide ongoing treatment free of charge, for example, until the public sector can and does take over the payment for the treatment according to laws and regulations. It may be necessary for the drug to go through a joint health technology assessment by Nordic countries, Joint Nordic HTA-Bodies (JNHB, formerly FINOSE), before the public sector can or will decide whether to cover the costs of the treatment in the respective country. The company can also decide to stop providing continued treatment free of charge. This poses a risk of treatment disruption. If the company wishes the public sector to continue paying for the treatment, the regulation No. 1414/2020 on the pricing of medicines and patient co-payments applies. It cannot be assumed that the public sector will take over the payment for the treatment without prior approval of payment participation in one of the reference countries and/or a joint health technology assessment by Nordic countries and/or an agreement on the price of the medicine. It should be noted that it is the responsibility of the treatment physician, according to the regulation, to inform the patient, before starting the use of the medicine through NAM, that continued treatment and state reimbursement for the medication cannot be guaranteed after NAM concludes. Therefore, it is important to address all loose ends before starting the treatment. Broadly speaking, the company has two options:

	1. **Market the Medicine:** The company applies for pricing and reimbursement to the Medicines Agency. The decision is based on factors such as the benefit of the treatment, the status of reimbursement in reference countries (Nordic countries), and cost/price agreement. 2. **Use the Exemption System:** The company applies for the maximum wholesale price for the exemption medicine to the Medicines Agency, and the medicine is listed as an exemption medicine in the drug price list. The treatment physician applies for individual reimbursement to the drug committee of Landspitali, and the medicine is prescribed through the prescription system.
What are the requirements for labelling and patient information leaflets after a company decides to terminate a programme?	If the drug is not marketed, i.e., it is an exemption drug – there are no requirements for labelling and patient information leaflets for exemption drugs. When the drug is marketed – the drug must meet the requirements for labelling and patient information leaflets. See rules and exemptions regarding labelling here. Attention is drawn to the project for electronic patient information leaflets for H-marked drugs, here.

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