Early Access for Compassionate Use in Europe

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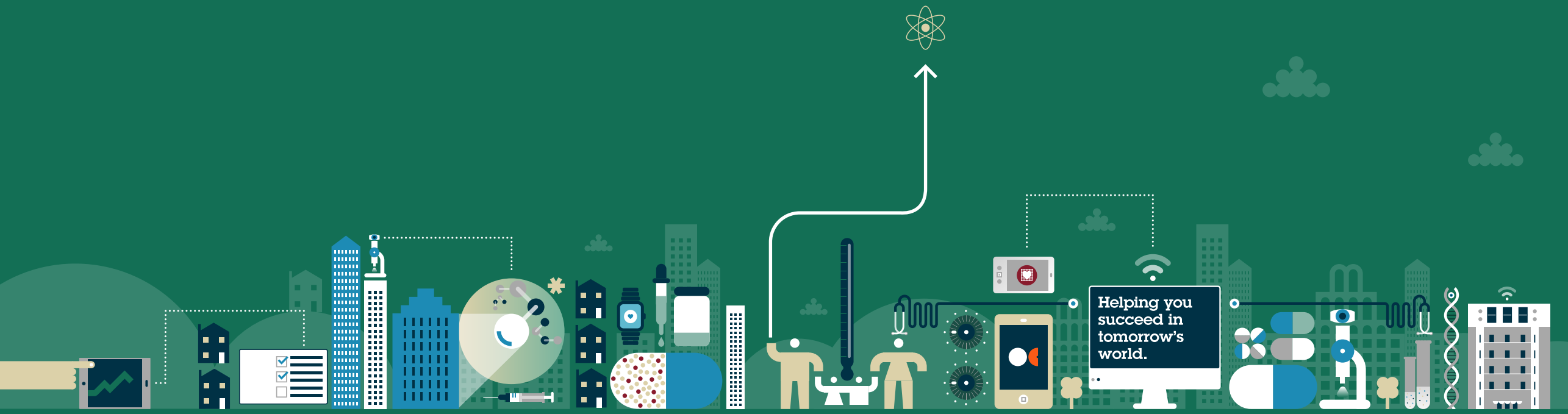

Introduction

European institutions are committed to enabling early access to new medicinal products, particularly for patients who face unmet medical needs and for products that are of a major interest for the public health.

In this regard, European Union (EU) pharmaceutical legislation includes several provisions to foster patients' early access to new medicinal products that address public health needs such as compassionate use, which allows the use of an unauthorised medicinal product for patients with an unmet medical need, under strict conditions.

The EU legal basis relating to compassionate use is provided for by:

- Article 5 of Directive 2001/83/EC: "A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive (requirement for a Marketing Authorisation (MA)) medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility."
- Article 83 of Regulation (EC) no. 726/2004: "By way of exemption from Article 6 of Directive 2001/83/EC [requirement for a MA], Members States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) [mandatory scope for the centralised procedure] and (2) [optional scope for the centralised procedure] of this Regulation available for compassionate use …'Compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3(1) and (2) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials."

This EU regulatory landscape is to be updated with the ongoing revision of pharmaceutical legislation, which is today under the European Council's review.

The UK's regulatory system regarding medicines has its origins in pre-Brexit EU legislation and has been supplemented by UK specific regulations and guidance.

Implementing compassionate use frameworks in their respective jurisdictions, the EU Member States must also consider the EMA Guideline on Compassionate Use of Medicinal Products.

Compassionate use regulations can provide for specific early access regimes to the benefit of individual patients or groups of patients.

For the purpose of this publication:

- "Compassionate use" is generally understood as a specific national regime allowing one or many individual named patients to have access to an innovative medicinal product before its approval through a standard marketing authorisation.
- "Early access" is generally understood as a specific national regime allowing a group or "cohort" of eligible patients to access to an innovative medicinal product before its approval through a standard marketing authorisation.

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Introduction

It can be summarised this way:

"Compassionate use" = Making a pharma product available for compassionate reasons to a group of patients:

- with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and
- who cannot be treated satisfactorily by an approved pharma product

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- Derogations to the regulatory product approval ("**marketing authorisation**")
- For patients facing unmet medical needs

Possibilities for making available a not-yet-approved pharma product under special regulatory regimes other than **clinical trials**

No full harmonisation at European level

Specific countries' regulations

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Belgium

Early Access and Compassionate Use

Belgian drugs agency **FAMHP** can authorise:

Compassionate use programmes for a "cohort" of patients

- For a product not yet covered by a marketing authorisation
- Per the initiative of FAMHP itself, per the request of the Ministry of Health, or per the application of the pharma company

Medical need programmes for a "cohort" of patients

- For a therapeutic indication not yet covered by the marketing authorisation of the product
- Per the initiative of FAMHP itself, per the request of the Ministry of Health, or per the application of the pharma company

- Pharma company must make the product available **free of charge**
- No reimbursement by the Belgian health insurance programme **INAMI**
- Can continue after marketing authorisation: until product admission to standard reimbursement

In addition to both programmess, prescribers can also use the Product for their individual patients:

- Who are not included into the cohort of the compassionate use programmes or medical needs programmes
- In urgent situations (generally, risk of death)
- Upon the individual patients' express consent

Belgium

Early Access and Compassionate Use

1. What are the laws or other mandatory rules that cover early access and compassionate use, if any?

In Belgium, early access is governed by the Medicines Act, of 25 March 1964, and the Royal Decree of 14 December 2006 regulating medicinal products for human use, known as the Medicines Decree.

Belgium has created a number of different early access regimes for individual patients and for groups of patients.

Among those, two specific systems can be compared to those available in other EU Member States, the Compassionate Use Programme (CUP) and the Medical Need Programme (MNP).

The following developments will concern the CUP and MNP procedures but there are additional specific local requirements to obtain a non-authorised medicinal product for patients, for example:

- Individual authorisation for a patient to be included in an ongoing clinical trial in Belgium.
- Urgent situations exempted from a CUP authorisation.
- The new article 105/1 of the Medicines Decree allowing for the import and distribution of unauthorised medicines under specific circumstances.

2. What kind of patients or diseases can enter into an early access or compassionate use programmes?

These programmes are used in case of an unmet medical need when the CUP and MNP patient population has a life-threatening, chronic or seriously debilitating disease that cannot be satisfactorily treated with a product that is licensed and reimbursed for this use and is commercially available in Belgium.

CUP can be used for non-authorised medicinal products and for a group of patients with a life-threatening disease, a chronic disease or a seriously debilitating disease that cannot be satisfactorily treated with a product that is already commercially available in Belgium.

MNP can be used for medicinal products authorised in Belgium and for a group of patients with a life-threatening disease, a chronic disease or a seriously debilitating disease that cannot be satisfactorily treated with a product that is already commercially available in Belgium but doesn't cover the MNP "indication" requested.

3. Which medicinal products can be made available in this way?

For the CUP, the medicinal product must either be undergoing clinical trials (CTs) or must be the subject of a centralised marketing authorisation application (MAA) submitted to the European Medicines Agency (EMA).

For the MNP, the medicinal product must either (i) be the subject of an ongoing MAA or granted MA but the medicinal product is not yet marketed with the MNP indication (so, the product is commercially available in Belgium for a previous indication but the reimbursement procedure for the MNP indication is ongoing) or (ii) clinical evidence has been generated in on-going CTs for the MNP indication. However, the modification in the dosing regimen is not regarded as a new-

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Early Access and Compassionate Use

not-yet authorised indication of an already authorised medicinal product that may qualify for an MNP application.

In addition, the medicinal products used in CUP and MNP need to be compliant with additional requirements:

- The label of the medication must be compliant with annex 13 of the Good Manufacturing Practice Guidelines, volume 4, including the statement “CUP/MNP – cannot be sold” in the three national languages (Dutch, French and German).
- A labelling derogation (English labelling) is possible if the patient does not take the medication at home and if the hospital staff that is in contact with the product understands the English language. If the patient takes the medicinal products home, the hospital pharmacist can stick labels in the three national languages. These derogations should be notified in the cover letter of the application.

4. How do early access and compassionate use programmes work?

The Belgian healthcare regulator may, upon the favourable opinion of an ethics committee and of the FAMHP's internal Commission for Medicinal Products for Human Use (CMH), set up the CUP or MNP either at its own initiative or at the request of the minister of health, the MA applicant, the manufacturer, the importer or the sponsor. The application dossier must be submitted to the FAMHP via the Common European Submission Platform (CESP). The applicant will then designate the treating physician. Both programmes, when set up by the FAMHP, only come into force once a "cohort" has been allocated to it. On a general note, only one indication can be considered per programme.

The applicant must in both cases communicate the application form via the CESP to the minister of health or its delegate. The dossier will then be communicated from FAMHP to an ethics committee, who will proceed to the evaluation of the programme from an ethical point of view and to the CMH.

The applicant will be informed of the eventual approval of the application via FAMHP.

For completeness, it is possible to set up a MNP for a combination of medicinal products for a new indication provided that all conditions for an MNP are fulfilled for unmet need as well as benefit and risk balance.

5. Who can enter a patient within an early access and compassionate use programme?

If a CUP or MNP has been set up, any Belgian physician can submit an application to the responsible physician of the programme to have one or more of their patients included in that programme.

The treating physician will have to send a motivated request to the responsible physician. In his request he or she declares that:

- He or she is aware of being personally responsible for the use of a yet unauthorised medicinal product.
- The disease for which the medicinal product shall be used is either a chronic

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Early Access and Compassionate Use

seriously debilitating or life-threatening disease and cannot be treated satisfactorily using a medicinal product marketed in Belgium that is authorised for treating this disease – the physician will need to give a description of the disease.

- He or she shall clearly and fully inform the patient concerned or his or her representative under the Act of 22 August 2002 on patients' rights, of all the terms and conditions of the programme.
- He or she shall ask as soon as possible and at the latest before the start of the treatment using the medicinal product concerned for the written consent of the patient or of his or her representative to participate in this programme.

The responsible physician shall check the conformity of each individual request with the programme and will inform the treating physician of his decision as soon as possible. In case of refusal, the reasons will be explained.

The applicant for a CUP or CMH procedure is responsible for programme execution, the designation of a responsible physician in charge of the inclusion of patients, keeping a central register of patients included and the recording of anonymised suspected serious adverse effects. The designated responsible physician is in charge of checking the request by the treating physician to include a patient in the programme and of sending adverse reactions to the CUP or CMH applicant.

If there is a shortage in stock of the programme medicinal product, it must first be ensured that patients that are already included can continue their treatment as long as they benefit from it. If this means that temporarily no new patients can be included, the programme should be put on hold. The FAMHP will need to be informed as soon as possible about an upcoming shortage in stock.

6. Who is the issuer and the recipient of the application? What role does the national authority have in the process? What are the evaluation timelines?

The procedure to be followed in Belgium for a CUP or MNP is respectively set out in articles 106 and 108 of the Medicines Decree.

For both CUP and MNP, the application will need to be submitted to the minister of health or their delegate, in practice the FAMHP, which includes an opinion of an ethics committee.

The following is required in the application:

- Clinical justification for the application.
- The period during which the programme shall take place.
- The conditions of use and indication for which the medicinal product shall be made available.
- The conditions of distribution.
- The criteria according to which patients can be included in the programme.

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Early Access and Compassionate Use

- The physician responsible for the programme.
- A standardised "informed consent" form for the patient to be submitted by the treating physician to the patients entering the programme (the FAMHP published templates for informed consent that could be adapted for compassionate use programmes).
- How to deal with unused medicinal products.
- The information for registration of suspected unexpected serious adverse reactions (including the list of expected adverse reactions).

In addition, the CUP or MNP applicant must specify whether it requests the intervention of the compulsory health insurance for reimbursement purposes.

The FAMHP will contact the CUP or MNP applicant within six working days to confirm the completeness of the application. If the request is not complete, the applicant will be contacted with a list of missing items that needs to be submitted within 30 days. If the request is complete, the starting date of the procedure is confirmed to the applicant by email within three days.

The FAMHP then forwards the application to the EMA. It may request, in consultation with EMA and the applicant, an opinion from the Committee for Medicinal Products for Human Use (CHMP).

The minister of health must adopt a decision on the compassionate use programme within 55 business days from the decision on the admissibility of the request, failing which, the decision is deemed positive.

Decisions are published five days later on the website of the FAMHP and are regularly reassessed.

7. Can a medicinal product under the early access or compassionate use programmes be sold or must it be supplied for free?

For both the CUP and MNP, the medicinal product must be made available by the company to the patient free of charge.

The provision of the medicinal product to the patient includes the medicinal product, its preparation in pharmacies and its administration – such as infusion or injection – to the patient. The costs connected with the provision of the drugs such as an outpatient stay or hospitalisation should be borne by the patient.

8. What tax treatment is applied to the company for the supply of medicinal products under early access and compassionate use programmes?

No pharma-specific tax rules exist in Belgium yet, regarding the use of medicines for compassionate use. General tax rules are applicable.

9. How can data obtained during an early access or compassionate use programme be used?

Data obtained within a compassionate use programme does not replace data required for the MA procedure.

From a methodological point of view, clinical trials are the only means of obtaining reliable

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Early Access and Compassionate Use

and interpretable efficacy and safety data for a medicinal product. Although safety data can be collected during a compassionate use programme, such programmes cannot replace CTs for investigational purposes.

Compassionate use is not a substitute for properly conducted trials. However, data collected during these programmes that are necessary for the conduct of the programme (for example, to check the inclusion or exclusion criteria, to follow up the benefit-risk of a patient and pharmacovigilance data) could be used to enlarge the understanding of the treatment.

Patients should always be considered for inclusion in CTs before being offered inclusion into a compassionate use programme.

Those responsible for the compassionate use programme must retain the data for at least 10 years after the termination of the programme, but must delete the data after a period of 30 years from the date of registration.

10. Is there any provision for early access and compassionate use of medical devices?

Presently, in Belgium, the CUPs and MNPs are limited in scope to medicinal products. However, comparable programmes are in place for medical devices to tackle unmet medical needs or public health crises.

'Orphan devices'

A high level of clinical evidence is required to place medical devices on the market. Pre-market clinical investigations of high-risk devices face rigorous tests when intended for use for rare diseases and conditions, or specific indications of rare cohorts of patients with an otherwise non-rare disease or condition. "Orphan devices" can be crucial to fulfil an otherwise unmet medical need and may be granted market access with acceptable limitations in the amount and quality of pre-market clinical data, as long as appropriate measures are implemented.

An EMA-led system is being put in place to grant orphan status to some higher-risk medical devices and provide scientific advice during their clinical evaluation, with a view to accelerating and facilitating their placement on the market. However, this does not grant an authorisation to place the products on the market prior to affixing the CE marking of conformity.

Request for exceptional use and special measures during the Covid-19 pandemic

Article 59 of Regulation (EU) 2017/745 on medical devices provides that, by way of derogation, the placing on the market can be authorised if it is in the interest of public health or patient safety or health.

A request for exceptional use can be sent to the FAMHP, which will authorise the placing on the market and putting into service on Belgian territory of a non-CE-marked device. The request must be justified and in the interests of public health or patient safety or health. Therefore, no derogation is possible

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Early Access and Compassionate Use

for any off-label use of medical devices, particularly in the absence of an alternative, which refers to any other device, product, or treatment that could achieve a similar purpose. An alternative is not necessarily a device with exactly the same characteristics. Additionally, it must be demonstrated that the expected benefit is significant due to the use of the device compared with the alternative diagnoses or treatments available. More specifically, there are two forms of derogations: derogation for individual devices for a specific patient ("compassionate use") and national derogation for a device.

The form must be completed by both the applicant (manufacturer, authorised representative or a third party mandated by them) and the physician concerned.

Additionally, in the context of the Covid-19 pandemic, special measures were adopted by the Belgian legislator to address crucial medical devices shortages.

An alternative test protocol (ATP) was implemented during the pandemic to address the overwhelming demand for surgical face masks. The use of surgical masks without the necessary declarations, certificates and test reports under European or international standards was nonetheless authorised, provided that the results of bacterial filtration efficiency and bacterial pressure (the most important parameters given the context) were examined. As an exceptional and temporary measure, surgical face masks without the required CE marking were accepted, provided these products were made available only during the crisis and did not enter regular distribution channels.

Similarly, the validation procedure for SARS-CoV-2 antigen self-tests with a CE certificate was temporarily removed.

France

Early Access and Compassionate Use

French drugs agency **ANSM** can authorise:

Compassionate Use

- Per application of prescribers for their individual named patients
- As many authorisations as patients for whom a prescriber requests a compassionate use

Early Access

- Per application of pharma company for a "cohort" of patients
- One single authorisation for all eligible patients

- Protocol for product use plus follow-up based on patients' data report (France's drug regulator ANSM plus pharma company)
- For specific non-approved therapeutic indications
- Product sold by pharma company to hospitals at a **free** price:
  - **Fully reimbursed** by the French national health insurance programme **AM**

  But:

  - Claw-back system (rebates paid each year by pharma company to **AM** based on volumes and sales turn over plus ultimate rebates at product admission to standard reimbursement based on the difference between the fee price versus regulated price
- Can continue after marketing authorisation: until product admission to standard reimbursement

France

Early Access and Compassionate Use

1. What are the laws or other mandatory rules that cover early access and compassionate use, if any?

In France, there are two sets of regulations:

- The “early access” regulatory framework set forth in article L.5121-12 of the French Code of Public Health (FCPH).
- The “compassionate use” regulatory framework detailed in FCPH, article L.5121-12-1.

France has always made these regimes a priority in order to facilitate access to innovative products for patients with unmet therapeutic needs.

Formerly called the authorisations for a temporary use (ATU) regime, it has been called the early access and compassionate use regime since the Law of 14 December 2020 and the regulations for its implementation such as the Decree of 30 June 2021.

The main points to consider differentiating the early access and compassionate use regimes are the related prior administrative authorisations that are required, by way of derogation to the general principle that no medicinal product can be placed on the market without a marketing authorisation:

- Early access authorisations (EAAs) can be granted by the French National Authority for Health (HAS), further to the application of a pharma company for a group of patients.
- Compassionate use authorisations (CUAs) can be granted by the French Health Products Authority (ANSM), further to the application of the physician who practices in a public hospital, for his/her individual named patients.

2. What kind of patients or diseases can enter into an early access or compassionate use programme?

Both EAAs and CUAs are focused in scope on the diseases and the related available therapies.

Early access authorisations

EAAs can be granted for medicinal products on an exceptional basis and for specific therapeutic indications that are not yet approved by a standard marketing authorisation (MA) – but the medicinal products can be approved by a MA for other therapeutic indication – subject to the following conditions:

- The product aims at treating a serious, rare or disabling disease.
- There is no appropriate treatment.
- The treatment cannot be postponed.
- The efficacy and the security of the medicinal product are "highly presumed" on the basis of clinical studies results.
- The medicinal product can be considered as innovative, in particular compared to other relevant therapies.

France

Early Access and Compassionate Use

Compassionate use authorisations

CUAs can be granted on an exceptional basis and for specific therapeutic indications only for unapproved medicinal products subject to the following conditions:

- There is no on-going research on patients for the product following a commercial purpose (such as clinical studies sponsored by pharma companies); however, by way of derogation, a CUA can be granted although there is research on patients for commercial purposes, if the named patient cannot be enrolled in the research and if their treatment cannot be postponed.
- The named patient suffers a rare, or serious or disabling disease.
- There is no appropriate treatment.
- The efficacy and the security of the medicinal product are highly presumed on the basis of available clinical data.

3. Which medicinal products can be made available in this way?

It's a matter more of therapeutic indication than of the product. Both EAAs and CUAs are focused on therapeutic indications, which are not yet approved through a standard MA.

Early access authorisations

An EAA can be granted by the HAS for a product to a pharmaceutical company only for one therapeutic indication that is:

- Not yet approved through the standard MA of the product but provided that the company (the applicant for the EAA) commits to submit an application for approval of the therapeutic indication via the MA procedure within a period determined by the HAS (with a maximum of two years from the granting of the EAA (known as the pre-MA EAA).
- Already approved under a standard MA but not yet admitted to reimbursement through the French Health Insurance Programme, if the company (the applicant for the EAA) commits to submit an application for the therapeutic indication admitted to reimbursement within one month from the granting of the MA (known as the post-MA EAA).

Compassionate use authorisations

A CUA can be granted by the ANSM further to the application of a physician (prescriber) for a named patient only:

- For the use of a medicinal product which is not approved in France.
- For the use of a product that is already covered by a MA but is no longer commercialised if the therapeutic indication for which the product is to be used under the CUA is not approved by the MA of such product.

France

Early Access and Compassionate Use

4. How do early access and compassionate use programmes work?

In principle, EAAs and CUAs are both granted together with an approved protocol for the therapeutic use (PTUD) of the medicinal product and for the collection of the related patients' data that the pharmaceutical company must implement.

Patient data collected under the PTUD will relate to the efficacy of the product, the adverse reactions, the real conditions of use of the product and the characteristics of the patients benefiting from the product under the EAA or the CUA. Subject to a few exceptions, the costs generated by the collection of such data must generally be incurred by the pharma company.

Early access authorisations

- An EAA is granted to a pharmaceutical company by the National Authority for Health together with a PTUD, which is drafted by the company in alignment with the ANSM.
- In an application for a pre-MA EAA, the HAS decision must be based on the prior opinion of the ANSM. Given that no MA has yet been granted, the ANSM is required to confirm in its prior opinion that the efficacy and the security of the product are highly presumed.
- The product must be available for supply at the latest two months after the granting of the EAA.
- The eligible patients must be informed by the prescribers that the product is used under an EAA, detailing the risk exposure and possible constraints, as well as the benefits expected from the product.
  The prescriptions must clearly mention "off-label prescription authorised under an EAA".
- EAAs are granted for a period determined by the HAS (a maximum of one year) and can be renewed.
- EAAs can be suspended or withdrawn by the HAS if the conditions for their granting are no longer met (for example, MA for the product or admission to reimbursement of the therapeutic indication at stake); the company does comply with its obligation to submit an application for a MA for the product or its obligation to file an application to get the therapeutic indication admitted for reimbursement; or there are deviations from the PTUD, safety issues with the product, negative opinion or refusal for the MA.

Compassionate use authorisations

- CUAs are granted to prescribers by the ANSM together with a PTUD. Prior to the granting of a CUA, the ANSM must inform the company that holds the rights pertaining to the product at stake.
- Products under CUAs can only be supplied to the public hospital where the prescriber – the holder of the CUA – has their practice.
- If the CUA is granted by way of derogation in case of an ongoing research, the costs generated by the PTUD must be incurred by the company. The named patient must be informed by the prescriber that the product shall be used out of any MA but under a CUA and given an explanation of

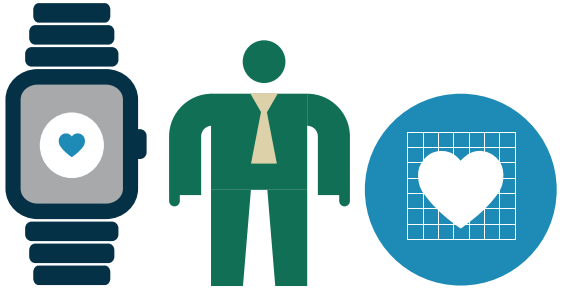
France
Early Access and Compassionate Use

the risk exposure and possible constraints as well as the benefits expected from the compassionate use of the product.

- The prescriptions must clearly mention "off-label prescription under a CUA".
- CUAs are granted for a one-year period and can be renewed.
- CUAs can be suspended or withdrawn by the ANSM if the conditions for their granting are no longer met, or in the event of safety issues.

5. Who can enter a patient into an early access or compassionate use programme?

- For products under EAAs: unless otherwise determined in the PTUD, any physician can prescribe the product for any eligible patient, but the product can be delivered only by pharmacies of public hospitals.
- For a product under a CUA: only the public hospital physician to whom the CUA has been granted can prescribe the product, and only for the named patient referred to by the CUA.



6. Who is the issuer and the recipient of the application? What role does the national authority have in the process? What are the evaluation timelines?

- EAAs: The applicant (then the holder) is the company holding the rights for the product. The HAS is the competent authority for granting EAAs and the ANSM is involved for the validation of the PUTD. It's a three-month process as from the receipt of a complete application file, which can be extended to one month if the HAS has too many EAAs applications to assess.
- CUAs: The applicant (then the holder) is the physician of a public hospital who is responsible for the treatment of the concerned individual named patient. The ANSM is the competent authority for granting CUAs. The pharma company holding the rights for the products is involved for the PTUD. There is no regulatory timeframe for the granting of a CUA as from the receipt of a complete file. It depends on the urgency and on the knowledge on the product at stake.

France

Early Access and Compassionate Use

7. Can a medicinal product under the early access or compassionate use programmes be sold or must it be supplied for free?

Medicinal products under EAAs and CUAs can be sold to public hospitals in France. There is no obligation to provide these products for free.

EAAs and CUAs are granted for specific therapeutic indications:

- If the product is already covered by an MA approving another therapeutic indication and is eligible for reimbursement for such a therapeutic indication, a regulated price has been determined for the product through a pricing agreement between the pharmaceutical company and France's pricing agency the Economic Committee for Healthcare Products. In this instance, the product ordered by the hospitals for use under an EAA is sold at the regulated price. This does not apply to products under CUAs, as these programmes cannot be granted for products that are already covered by an MA the products are necessarily not yet eligible for reimbursement.
- If the product is not yet eligible for reimbursement for any other therapeutic indication, the general principle provides that the product can be sold to public hospitals at a price freely determined by the pharmaceutical company (in some situations, however, the French Ministry of Health can determine a maximum price). The hospitals can then charge back a free price to the social-security administration through a specific regime of the French Health Insurance Programme. This applies to both EAAs and CUAs.

However, French legislation requires that pharmaceutical companies pay a rebate on the turnover they made from sales of products under EAAs or CUAs each year. Pharmaceutical companies are required to pay back to the French social-security administration some part of the profit they generate on their sales. In summary:

- Each year, pharmaceutical companies must declare to the administration the turnover they made the year before on their sales of products under EAAs and CUAs as well as other relevant information.
- On the basis of these declarations, the administration calculates the mandatory rebate that must be back-paid by the company to the social-security administration. This is based on progressive rating scales that are determined by the Ministry of Health.

French legislation provides for a clawback system but only for products sold at a free price during EAAs or CUAs. Under this system, the social-security administration can recover some part of the public expenses that they have incurred covering the full free price of the products as soon as a lower regulated price has been determined when the products are eligible for standard reimbursement. This adjustment can be summarised this way:

If the turnover generated by the company from its sales at the free price during the EAA or CUA period exceeds the turnover from the same sales period recalculated at the regulated price, the company must make additional payments to the social-security administration. These payments are calculated based on the difference between the turnover at the free price and the turnover at the regulated price.

France

Early Access and Compassionate Use

8. What tax treatment is applied to the company for the supply of medicinal products under early access and compassionate use programmes?

VAT. There is a lower VAT rate in France (2.1%) for the sales of medicinal products which are eligible for reimbursement in standard market conditions in France. This lower VAT rate also applies to the sales of products under EAAs or a CUAs.

Special pharmaceutical taxes. French law also provides for a set of additional taxes that are specific to the sales of reimbursed medicinal products. Some of them apply to the sales of products under EAAs or CUAs:

- "Turnover tax". A specific tax that pharmaceutical companies must pay each year. The tax is based on the turnover made by the companies on their sales of reimbursed medicinal products. Turnover tax applies to the sales of medicinal products under EAAs (sales of products under CUAs stay out of scope).
- "Contribution M". Another specific pharmaceutical tax that aims at balancing the budget of the National Health Insurance Programme each year. In some situations, it can apply to the sales of products under EAAs or under CUAs.

9. How can data obtained during an early access and compassionate use programme be used?

Data collected under PTUDs (both EAAs and CUAs) is processed in order to draft the reports on the use of the product on the patients for the competent authorities – the HAS and ANSM.

This data can also be used for supporting MA files or "transparency files" (products dossiers for reimbursement eligibility), but do not replace the standard clinical data required for the MA procedures.

The processing and collection of data must comply with the General Data Protection Regulation and French data privacy law.

The operator that qualifies as a data controller (depending on the respective roles of pharma companies and hospitals in EAAs and CUAs) should either:

- Submit an application to the French Data Privacy Authority (CNIL) for a prior authorisation as patients' heath data qualify as "sensitive data" which the collection and processing must be authorised under French law; or (as an exception to this prior-authorisation principle); or
- File a self-certification of compliance with the CNIL, if applicable, using a methodology of reference. CNIL guidelines out-line the requirements for securing privacy in the collection and processing of patients' health data. Data controllers can self-certify their compliance with these guidelines instead of applying for prior authorisation.

The patients should confirm their consent for the collection and processing of their personal health data and should be informed of their related rights.

10. Is there any provision for early access and compassionate use of medical devices?

No, EAAs and CUAs are limited in scope in France to medicinal products.

Germany

Early Access and Compassionate Use

German drugs agency **BfArM** and German vaccines agency **PEI** can authorise:

Early Access Programmes for a "cohort" of Patients

- Generally per the application of the pharma company
- One single authorisation for a cohort of eligible patients

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- Early access programme
- Product made available free of charge (no reimbursement by the German health insurance programme GKV)
- Can continue after marketing authorisation: until product admission to standard reimbursement (admission goes fast)

Germany

Early Access and Compassionate Use

1. What are the laws or other mandatory rules that cover early access and compassionate use, if any?

The main statutory rule in Germany for early access programmes is section 21 paragraph 2 Number 3 of the Medicinal Products Act (AMG). This legal provision expressly refers to article. 83 of the Regulation (EC) No. 726/2004.

In addition, the Federal Ministry of Health has issued the Ordinance on Medicinal Products for Compassionate Use (AMHV) detailing the procedure of early access programmes in Germany.

2. What kind of patients or diseases can enter into an early access or compassionate use programme?

According to German law, patients who suffer from a seriously disabling illness or whose illness is life threatening and cannot be treated satisfactorily with an authorised medicinal product qualify for an early access programme.

Early access programmes in Germany are only applicable to programmes intended to treat a cohort of patients.

There is no treatment of an individual patient under early access programmes.

Clinical trials have precedence over hardship programmes because the latter are not intended to be a substitute for clinical trials.

3. Which medicinal products can be made available in this way?

Early access programmes can only be put in place for medicinal products that are expected to help patients with life-threatening, long-lasting or seriously disabling illnesses.

The medicinal product must either be the subject of an application for a marketing authorisation or must be undergoing clinical trials.

4. How do early access and compassionate use programmes work?

If a pharmaceutical company wants to conduct an early access programme in Germany, they must submit a notification to the competent higher federal authority. (Information on the notification process is set out in the "Guideline for Notification of a Compassionate Use Programme" (Federal Institute for Drugs and Medical Devices (BfArM).

The pharmaceutical company must also appoint a "responsible person" who bears the overall responsibility for the early access programme (see section 7 of the AMHV). The "responsible person" is not defined by German law and, therefore, can be either a natural or a legal person (usually the pharmaceutical company will be responsible person). However, the responsible person must have a representative registered in a member state of the European Union if the responsible person does not have their registered place of business in the European Union.

Germany

Early Access and Compassionate Use

The competent authority will confirm receipt of the notification. The early access programme can be commenced as soon as the confirmed notification has been received and the competent higher federal authority has raised no objections, according to section 4 paragraph 2 of the AMHV.

The programme automatically ends after one year at the latest – in order to restrict the supply of unauthorised medicinal products. Thereafter, the programme must be submitted again.

The competent authority publishes all ongoing early access programmes on its website; for example, the ongoing early access programmes of the BfArM.

5. Who can enter a patient within an early access or compassionate use programme?

Patients must speak to their treating physician in order to enter an early access programme, as medicinal products that have not been authorised are first made available to patients through clinical trials. The physician will first advise the patient on whether there is a suitable clinical trial in their country that they can enter. The physician will also advise the patient on early access programmes.

6. Who is the issuer and the recipient of the application? What role does the national authority have in the process? What are the evaluation timelines?

According to section 77 paragraph 1 of the AMG, the competent higher federal authority is the BfArM unless the Paul-Ehrlich-Institute (PEI) is responsible. The PEI is responsible for sera, vaccines, blood preparations, tissue preparations, tissues, allergens, advanced therapy medicinal products, xenogenic medicinal products and genetically engineered blood components.

The national authority is responsible for the confirmation of the notification.

The evaluation timeline is outlined in section 4 of the AMHV:

- The competent national authority confirms the notification no later than two weeks after receipt of the notification.
- In case of missing documents, the competent national authority also confirms no later than two weeks after receipt of the subsequent delivery.
- Special deadlines: 60 days for notifications concerning an advanced therapy medicinal product or a medicinal product that has not yet been assessed by the competent national authority in an authorisation procedure for a clinical trial in the same indication.

7. Can a medicinal product under the early access or compassionate use programmes be sold or must it be supplied for free?

Section 21 paragraph 2 No. 3 of the AMG stipulates that a medicinal product of an early access programme must be supplied for free.

Germany

Early Access and Compassionate Use

8. What tax treatment is applied to the company for the supply of medicinal products under early access and compassionate use programmes?

As the medicinal products are supplied free of charge, no tax is payable on them (section 1 paragraph 1 No. 1 Value Added Tax Act).

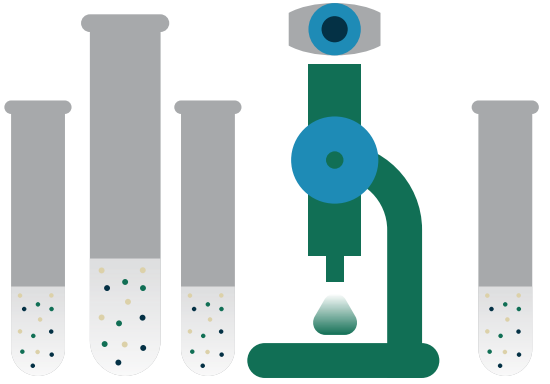
9. How can data obtained during an early access or compassionate use programme be used?

Early access programmes do not replace the standard clinical data required for the marketing authorisation procedures.
The data obtained in the context of an early access programme cannot be compared in terms of validity with the informative value of findings from clinical trials in accordance with the standards of a good clinical practice programme.

10. Is there any provision for early access and compassionate use of medical devices?

In principle, medical devices do not require a market authorisation such as medicinal products. To be placed on the market, medical devices must have undergone a conformity assessment procedure and be certified with a CE mark.

However, according to article 59 of the Medical Device Regulation (MDR), any competent authority can authorise the placing on the market or putting into service of a specific medical device for which the procedures referred to in the MDR article have not been carried out but the use of which is in the interest of public health or patient safety or health.



Italy

Early Access and Compassionate Use

Italian drugs agency **AIFA** can authorise:

Compassionate use	Early access "648 list"	Early access "AIFA 5% fund"	Non-repetitive use of advanced therapies
– Per the application of prescribers/hospitals: - For individual named patients, or - For a cohort of eligible patients	– Per the initiative of AIFA itself, or – Per the application of (i) patients associations (ii) prescribers/hospitalsor (iii) other public health bodies – For all eligible patients	– Per the application of prescribers and hospitals – For individual named patients	– Per the application of hospitals – For personalised therapies of individual patients
Product made available to Hospitals free of charge (no reimbursement)	Product sold by pharma company to hospitals: – at price negotiated with **AIFA**, and – fully reimbursed to hospitals by the Italian national health insurance programme "**SSN**"	Product sold by pharma company to hospitals: – at a price pre-approved by **AIFA**, and – fully reimbursed to hospitals by **AIFA** AIFA uses a special budget funded by the pharma companies (each pays to **AIFA** an annual contribution based on 7% of their ownmarketing budget)	Generally for cells therapies: – Production by authorised cells factory of pharma company – At hospitals' costs (no reimbursement by **AIFA** or **SSN**)

In some cases: can continue after marketing authorisation: until product admission to standard reimbursement

Italy

Early Access and Compassionate Use

1. What are the laws or other mandatory rules that cover early access and compassionate use, if any?

In Italy, there are three sets of regulations to foster patients' early access to medicinal products before approval through a marketing authorisation (MA) or to authorise medicinal products with an MA but for indications other than those expressly authorised (that is, "off-label use").

- The so-called "648 list" regulatory framework set forth in article 1, paragraphs 4 and 4 bis of the Law Decree n. 536/1996, converted by Law n. 648/1996 and in the ruling of the Ministry of Health of 20 July 2000 ("Provvedimento CUF").
- The so-called "AIFA 5% fund" (subsequently increased to 7%) regulatory framework detailed in article 48, paragraphs 18 and 19 (a) of the Law Decree n. 269/2003, converted by Law n. 326/2003.
- "Compassionate use" governed by the Decree of the Ministry of Health of 7 September 2017 which repealed the Ministerial Decree of 8 May 2003 (still in force with respect to compassionate use programmes activated before the entering into force of the decree on 2 December 2017).

2. What kind of patients or diseases can enter into an early access and compassionate use programme?

The 648 list

Patients can enter a programme if they have diseases that can be treated with medicinal products listed in the 648 list, approved by the Italian Medicines Agency (AIFA), and if no viable therapeutic alternatives are available. Alternatively, if there are therapeutic alternatives, patients can enter the programme for indications other than those expressly authorised, provided these indications are known and consistent with research conducted within the national and international medical and scientific community.

Patients must give written informed consent indicating their awareness of there being incomplete data regarding the safety and efficacy of the medicinal product for that therapeutic indication.

AIFA 5% fund

Patients with serious and rare diseases, and where the number of cases in a given population does not exceed the threshold of five cases per 10,000 people per year.

Compassionate use

Patients with serious or rare diseases, or tumours or life-threatening conditions for whom no viable therapeutic alternatives are available, or a patient who cannot be included in a clinical trial. Also, for the purposes of therapeutic continuity, patients already treated with clinical benefit in a completed clinical trial.

The ministerial decree of 7 September 2017, contains the following definitions:

- Rare diseases: a number of cases in a given population not exceeding the threshold of five cases per 10,000 people per year, included in either the European Medicines Agency list or the list of the national centre or rare diseased of the Istituto Superiore Sanità.
- Rare tumours: with an incidence of less than six cases per 100,000 per year.

Italy
Early Access and Compassionate Use

3. Which medicinal products can be made available in this way?

648 list

The following medicinal products can be included in the 648 list:

1. When there is no viable therapeutic alternative:
   - Innovative medicinal products authorised in other states but not in Italy.
   - Medicinal products not yet authorised but under clinical trials.
   - Medicinal products to be used for a therapeutic indication other than those authorised (“off label use”).

In all these cases, phase-two clinical trials results must be available.

2. When there is a valid therapeutic alternative:
   - Medicinal products to be used for a therapeutic indication other than those expressly authorised, provided that the indication is known and consistent with research conducted within the national and international medical-scientific community and according to economic parameters and appropriateness.

AIFA 5% fund

"Orphan" medicinal products for rare diseases and products that represent a hope for a cure, awaiting commercialisation, for particular and serious pathologies.

On 20 June 2023, AIFA published the access criteria to the 5% fund clarifying that the request for access can be made if all the inclusion criteria are met, while the presence of even one exclusion criteria precludes access to the fund.

AIFA's inclusion criteria are:

- Medicinal products for rare and particularly serious life-threatening diseases, provided that there is clinical urgency, and required on a nominal basis for each patient.
- Absence of a viable therapeutic alternative available on a reimbursable basis, including situations of non-response or absolute contraindication to treatments that may be available.
- Medicinal products where published efficacy and safety data are available at least from phase-two clinical trials or, in the case of rare diseases, considered to be of a sufficient level, which support the applicant's clinical report for each patient, based on the clinical condition, stage and rapid progression of the disease.
- For applications concerning rare diseases, documented inaccessibility to dedicated funds from patients' region of residence, if any.
- Documented denial or inability to place the patient in a compassionate use programme or in an ongoing clinical trial.

AIFA's exclusion criteria preclude access through the 5% fund to medicinal products that are:

- Authorised in Italy for indications other than those proposed and required to be used not for a single patient but for a sub-population according to a specific protocol of use.
- Reimbursed by the National Health Service (NHS) or included in the 648 list or in class C (non-negotiated) or C, for the requested indication.

Italy
Early Access and Compassionate Use

– Unauthorised by the EMA's Committee for Medicinal Products for Human Use (CHMP) or withdrawn by the MA holder following ongoing evaluation by the CHMP or for inclusion in the 648 list for the requested indication.

Medicinal products with a major impact on the Fund may not be eligible for reimbursement, regardless of whether the inclusion criteria are met, due to the potential impact in terms of economic sustainability and distribution equity.

Compassionate use

The following medicinal products can be made available through compassionate use programmes:

– Medicinal products that are not yet authorised and are under clinical trials and manufactured in pharmaceutical sites or imported in accordance with the authorisation procedures and requirements provided for by the legislation in force.

– Medicinal products with an MA but that is for indications other than those expressly authorised ("off-label use").

– Medicinal products authorised but not yet available in the national territory.

These medicinal products shall:

– Be already the subject, in the same specific therapeutic indication, of ongoing or completed phase-three clinical trials or, in special cases of life-threatening disease conditions, of completed phase-two clinical trials.

– Have data available on these completed phase-three or two trials that are sufficient to make a favourable opinion on the efficacy and tolerability of the medicinal products requested.

– Be provided with production certification in accordance with good manufacturing practice.

In the case of rare diseases or tumours, at least phase-one clinical trials need to be available. These need to have been completed and have documented the activity and safety of the medicinal product, at a given dose and schedule of administration, also in indications other than the one required for compassionate use.

4. How do early access and compassionate use programmes work?

648 list

Medicinal products that obtain a favourable opinion from AIFA's Scientific and Economic Committee for Medicines (CSE) are included in a special list and can be prescribed at the sole expense of the NHS for all subjects in the national territory who are affected by the pathology identified in AIFA's provision. Before the inclusion of the medicinal products in the list, the price needs to be negotiated with AIFA according to a simplified and accelerated procedure. The medicinal products remain registered in the 648 list while the needs that determined their inclusion persist or until a new provision by AIFA.

General conditions to prescribe medicinal products in the 648 list are the following:

– Written informed consent from the patient, which shows that the patient is aware of the incompleteness of the data relating to the safety and efficacy of the medicinal product for the proposed therapeutic indication.

Italy

Early Access and Compassionate Use

- Treatment plan and prescription by specialized hospital or university facilities or by scientific hospitalization and treatment institutes.
- Dispensing through the pharmaceutical service of the prescribing facilities, where possible, or the pharmaceutical service of the local health authority where the patient resides.

AIFA 5% fund

AIFA's fund is in part financed by the pharmaceutical companies that pay an annual basis contribution. It is intended for the purchase of orphan medicinal products for rare diseases and medicinal products that represent a hope of cure for particular and serious pathologies. The request for access to the 5% fund is made on a nominal basis for each patient and is evaluated by AIFA. In order to be assessed, the request must contain all of the following information:

- Rationale supporting the proposed treatment including justification for the lack of a therapeutic alternative.
- Patient's clinical report (updated with the most recent clinical data).
- Proposed treatment plan (dosage, duration of therapy).
- Estimate of expenditure for the proposed treatment.

The request for access to the fund is assessed by AIFA, which expresses its opinion after verifying the existence of the conditions required by law.

However, the initiation of treatment does not require any prior authorisation by AIFA, since this authorisation relates solely to the reimbursement of the cost incurred by the hospital or the region. Having received the supporting documentation of the expenditure necessary for the treatment of the patient (which is advanced by the requesting regional health department), AIFA will reimburse the invoices already paid economically cover the expenditure.

Compassionate use

In Italy, there are two options to adopt compassionate use.

- An individual basis treatment (the “uso nominale”) that is “the compassionate use of medicinal products on an individual patient basis”, not within a defined clinical protocol of compassionate use.
- A defined therapeutic programme, which is implemented by a pharma company, with previous approval by AIFA. The company indicates the medicinal product that it intends to make available free of charge under the decree, also stating the period of presumed availability of the products (without prejudice to regulatory or security situations that may lead to early termination of the programme).

Access to compassionate use requires a favourable opinion from the competent ethics committee to which the clinical centre submitting the request belongs, subject to confirmation of the availability to supply the medicinal products free of charge by the pharma company.

Italy
Early Access and Compassionate Use

5. Who can enter a patient within an early access and compassionate use programme?

Early access 648 list

The medicinal product must be included in the 648 list. The inclusion in the 648 list can take place on the initiative of the CSE of AIFA or upon request of patient associations, scientific societies, health companies, universities, scientific hospitalisation and treatment institutes, or also physicians.

AIFA 5% fund

The request for access to the AIFA 5% fund is made by physicians, hospital pharmacists, health directors or administrative directors.

Compassionate use

The request to enter a compassionate use programme is made by:

- The relevant healthcare professional (HCP) or group of HCPs also working in different centres or groups for the individual patient not treated in clinical trials, or for the individual basis treatment or for therapeutic programmes.
- The HCP (single or group) for patients who attended a clinical trial that has demonstrated a profile of tolerability, safety and efficacy, such that there is an indication for continued care even after the clinical trial has ended.

6. Who is the issuer and the recipient of the application? What role does the national authority have in the process? What are the evaluation timelines?

648 list

The request for the inclusion of medicines in the 648 list is made by the subjects indicated in answer to question 5, and approved by the CSE of AIFA.

The application shall be submitted with the following documentation attached:

- A scientific report on the pathology representing its severity and the absence of a valid therapeutic alternative.
- A description of the proposed treatment plan.
- Indicative data on the cost of the treatment per patient (monthly or per course of therapy).
- The authorisation status of the medicinal product in Italy and abroad with indications of the manufacturing or supplying company.
- Available documentation such as scientific publications, the results of first and second phase clinical trials, also refer-ring to the quality and safety of the medicinal product and information concerning clinical trials still in progress.

The request is first evaluated by the support and coordination secretariat of AIFA's pre-authorisation area, which expresses a non-binding opinion, and then by AIFA's CSE, which expresses its final opinion.

Following the CSE's favourable opinion, the application is forwarded to AIFA's board of directors, which assesses the impact on pharmaceutical expenditure and decides on the reimbursability of the medicinal product. After the board's approval, the medicine can be included in the 648 list through a provision published in the Italian Official Gazette.

There is no timeline for the evaluation provided by law.

Italy
Early Access and Compassionate Use

AIFA 5% fund

The request for access to the AIFA 5% fund is made by the subjects indicated in answer to question 5, who need to register on the AIFA online services portal. Each region identifies a regional user approver who is responsible for enabling and disabling the administrative directors and health directors of the health facilities and each health facility has the role of a company user approver (AUA) who can enable or disable the physicians and pharmacists of their facility.

The prescription of the treatment is the sole responsibility of the treating physician. The initiation of treatment does not require any prior authorisation by AIFA, which evaluates that the request for access to 5% fund complies with the provisions set out in the law for the purpose of reimbursement of costs incurred within the limits of the approved budget.

Applications for reimbursement are made through an online AIFA's service and shall contain the following information:

- Rationale supporting the proposed treatment including justification for no therapeutic alternative.
- Patient's clinical report (updated with the latest clinical data).
- Proposed treatment plan (dosage, duration of therapy).
- Cost estimate for the proposed treatment.

The authorisation to access the 5% fund expires three months after the date of the authorization provision without the treatment having been started.

Compassionate use

The application is submitted by the subjects indicated in answer to question 5, in advance to the competent ethics committee for evaluation, with the following documentation attached:

- Clinical justification for the application.
- Dosage regimen and mode of administration demonstrated to be safe and active in the clinical trials on which the request is based.
- Degree of comparability of the patients included in the clinical trials and of those for whom the request is made or, for rare diseases and tumours only, the existence of at least one common mechanism of action that makes a clinical benefit foreseeable on the basis of the evidence available for the medicinal product.
- Relevant data on safety, tolerability and efficacy.
- Patient information template.
- Declaration of willingness of the manufacturing company to supply the medicinal product free of charge.
- Data collection arrangements.
- Declaration of assumption of liability by the health care professional (according to the relevant programme requested).

The ethics committee then relays its opinion to AIFA, with all the relevant documentation within three days from the adoption of the opinion for informational purposes. AIFA, if it deems it necessary for the protection of public health, can intervene in a restrictive manner and suspend or prohibit the use of the medicine.

Pharma companies that intend to activate compassionate use programmes in Italy must inform AIFA of the activation date (at least 15 days in advance) and closure of the program

Italy

Early Access and Compassionate Use

(at least 30 days in advance), indicating the medicinal product they intend to make available free of charge and declaring the period of probable availability for free supply.

7. Can a medicinal product under the early access or compassionate use programmes be sold or must it be supplied for free?

648 list

The medicinal product is sold by the pharma company to the hospitals at a price negotiated with AIFA according to a simplified and accelerated procedure, and fully reimbursed to hospitals by the NHS. It is free for patients.

AIFA 5% fund

The medicinal product is sold by the pharma company to the hospitals at a price pre-approved by AIFA and fully reimbursed to hospitals by AIFA. It is free for patients.

Compassionate use

Compassionate use involves direct and free delivery of the medicinal products by the pharma company.

8. What tax treatment is applied to the company for the supply of medicinal products under early access and compassionate use programmes?

648 list

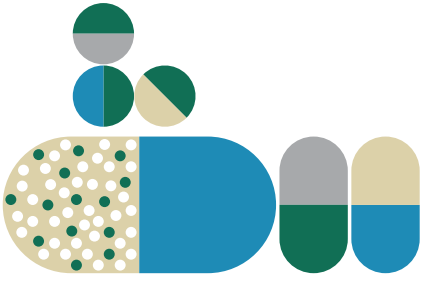
Medicinal products are sold by the pharma company at a price negotiated with AIFA (see answer to question 7).

AIFA 5% fund

Medicinal products are sold by the pharma company at a price pre-approved by AIFA (see question 7).

Compassionate use

Under article 27 of the Law Decree 23/2020 converted with amendments by Law no. 40/2020 and the subsequent Italian Tax Agency Ruling number9/E and number 26/E of 2020, the free supply of medicinal products for compassionate use is treated for VAT purposes as equivalent to their disposal. Therefore, on the one hand, the supply is excluded from the application of VAT and, on the other hand, the input VAT remains deductible. In addition, the value of the medicines sold does not contribute to the determination of the business income and the cost incurred for their purchase is deductible in the tax period in which the disposal occurs.



Italy
Early Access and Compassionate Use

9. How can data obtained during an early access and compassionate use programme be used?

The processing and collection of data must comply with the General Data Protection Regulation and the Italian Data Privacy Law.

648 list

No specific provision regulates the use of data related to medicinal products included in the 648 List.

However, for the sake of completeness, we highlight that the prescribing centre is required to send to AIFA the following data for each patient to monitor the medicines included in the list:

- Age and sex.
- Date of start of treatment.
- Clinical course according to the parameters identified.
- Adverse events.
- Date and cause of any interruption of treatment.
- Date of any termination of the treatment plan.

Failure to submit such data may lead to the exclusion of the medicines from the 648 list.

AIFA 5% fund

No specific provision regulates the use of data related to medicinal products available through the fund.

Compassionate use

Data obtained within a compassionate use programme does not replace data required for the marketing authorisation procedure, but may be used as supporting data for the latter.

10. Is there any provision for early access and compassionate use of medical devices?

Under Article 11, Paragraph 9 of Legislative Decree 137/2022, the Ministry of Health may authorise the use of medical devices that do not yet have a CE certificate for the treatment of individual patients. This can be done in exceptional cases of necessity and urgency, where there are no valid medical alternatives available. The authorisation process will be established by a ministerial decree and requires specific declarations from the manufacturers.

We are not aware of the effective publication of a “ministerial decree” on the matter, but the Ministry of Health has provided detailed guidelines for the compassionate use of medical devices.

Also, in this case, the HCPs involved in the programme who can legally represent the applicant sanitary facility and assume the relevant administrative responsibilities, in summary shall:

- Request to the Ministry of Health authorisation for the use of the medical device for a specific patient according to its proposed intended use.
- Submit a specific report to the Ministry of Health and the relevant ethics committee (also with patient data) as well as the declaration of the manufacturer on the status of the procedures for the assessment of conformity with respect to the intended use of the medical device.
- Wait for the ethics committee opinion and the Ministry of Health authorisation (within 30 days from the application).

Spain
Early Access and Compassionate Use

Spanish drugs agency **AEMPS** can authorise:

Compassionate use programmes for individual named patients

- Generally per application of prescribers/ hospitals:
  - For use of product out of an on-going clinical trial,
  - To frame "off-label" use,

  or
  - For "foreign medicines"
- As many authorisations as patients for whom a prescriber/hospital requests a compassionate use

Early access for a cohort of eligible patients

- Extension of individual compassionate use programmes per the hospital's requests, if the number of patients eligible to individual programmes is too significant
- AEMPS can grant a temporary"early access" authorisation to the sponsor of the clinical trial (or the applicant of the market authorisation) for a cohort of eligible patients

Product delivered by pharma company:

- At "reasonable free price" fully covered by the national health insurance programme **SNS**:
  - Controlled (compassionate use programmes can be terminated if excessive free price)
  - Aligned with regulated price, if any, for the "in-label" use
- Can continue after marketing authorisation: until product admission to standard reimbursement

Spain

Early Access and Compassionate Use

1. What are the laws or other mandatory rules that cover early access and compassionate use, if any?

Article 24 of Spanish Act 1/2015, of July 24, on guarantees and rational use of medicines and health products sets forth the guarantee of availability of medicines in specific situations and special authorisations.

Article 24 is developed by Spanish Royal Decree 1015/2009, of June 19, which regulates the availability of medicines in special situations including the use of compassionate medicines in Spain.

2. What kind of patients or diseases can enter into an early access and compassionate use programme?

Patients with treatment needs either due to suffering from a clinical situation without indicated therapy or due to having a compromised disease. A compromised disease is understood as one that is chronic or seriously debilitating or one that endangers the patient's life and cannot be treated satisfactorily with an authorised and marketed medicine.

3. Which medicinal products can be made available in this way?

Under article 2 of the decree, the following medicines can be made available through early access and compassionate use programmes:

- Medicines that are not yet authorised in Spain, but that are under clinical trials or subject to a marketing authorisation application in Spain – "proper compassionate use" strictly speaking.
- Medicines with a marketing authorisation in force is Spain, but for indications other than those expressly authorised – an "off-label use".
- Medicines authorised in foreign countries but not yet available and authorised in Spain – or "foreign medicines".

4. How do early access and compassionate use programmes work?

In Spain, there are a number of early access and compassionate use programmes in place.

Proper compassionate use programmes for medicines that are under clinical trials

- Authorisation of individualised access: A hospital or healthcare organisation (HCO) upon receipt of the approval of its governing body will need to make a request to the Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios) (AEMPS) for the authorisation of a medicine that is under a clinical trial to be used on a case by case basis and outside such clinical trial.
- Temporary authorisations: Further, AEMPS may issue a temporary authorization for an early access use of investigational medicines outside of a clinical trial, provided such use is foreseen for a significant group of patients.

Compassionate use programmes for off-label use of medicines

The use of authorised medicines under conditions other than those set forth in their technical specifications shall be exceptional and be limited to situations in which there is

Spain
Early Access and Compassionate Use

a lack of authorised therapeutic alternatives for a specific patient, taking into account, where appropriate, the restrictions applicable to the prescription of the medicine and the therapeutic protocol of the HCO.

The healthcare professional responsible for the treatment shall properly (i) justify the need for the use of the medicine in the clinical history of the patient and (ii) inform the patient about the potential benefits and risks of such use, obtaining their in-formed consent in accordance with the applicable law.

AEMPS may develop recommendations for the use of the medicine when there is a potential a risk to patients derived from the use of such medicine under conditions not contemplated in the technical specifications.

Compassionate use programmes of foreign medicines

- Procedure for individualised access to unauthorised medicines in Spain: The request for individualised access to a foreign medicine (not authorised in Spain) will be submitted to AEMPS by the health authorities of the Spanish autonomous communities and regions or by HCOs designated by them.
- Procedure for access to unauthorized medicines in Spain through a protocol of use: AEMPS may develop protocols to set forth the conditions for an early access use of a medicine not authorised in Spain when this medicine is expected to be used for a significant number of patients.

5. Who can enter a patient within an early access and compassionate use programme?

The person or entity responsible to enter a patient within a compassionate use programme will depend on the type of early access or compassionate use programme.

- Proper compassionate use programmes for medicines that are under clinical trials: the HCO, for individualised cases and compassionate use; and AEMPS, when the authorisation is given for an early access use to a significant group of patients.
- Compassionate use programmes for medicines off label: the healthcare professional responsible for the treatment of the patient. Such healthcare professional shall (i) obtain the prior written informed consent of the patient and (ii) follow the recommendations issued by AEMPS regarding the specific medicine, if any.
- Compassionate use programs of foreign medicines: the health authorities of the Spanish autonomous communities and regions or the HCOs designated by them.

Spain
Early Access and Compassionate Use

6. Who is the issuer and the recipient of the application? What role does the national authority have in the process? What are the evaluation timelines?

As stated, the issuer and the recipient may depend on the type of early access or compassionate use programme.

Proper compassionate use programmes for medicines that are under clinical trials

- Authorisation of individualised access: the issuer of the application is the HCO upon receipt of the approval of its manager body. The recipient of the application is AEMPS.
- Temporary authorisations: AEMPS may issue a temporary authorisation for the early use of investigational medicine outside of a clinical trial. An individual application from a HCO or a healthcare professional to AEMPS is not required in this case.

Compassionate use programmes for off label use of medicines

No individual application to AEMPS is required. The healthcare professional assumes the responsibility for treating his/her patient with the off-label medicine. However, AEMPS may develop recommendations for the use of such medicine.

Compassionate use programmes of foreign medicines

- Procedure for individualised access to unauthorised medicines in Spain: The request for individualised access to a foreign medicine (not authorised in Spain) shall be submitted to AEMPS by the health authorities of the Spanish autonomous communities and regions or the HCOs designated by them.
- Procedure for access to unauthorised medicines in Spain through a protocol of use: AEMPS may develop protocols to set forth the conditions for an early use of a medicine not authorised in Spain when the medicine is expected to be medicine for a significant number of patients.

7. Can a medicinal product under early access or compassionate use programmes be sold or must it be supplied for free?

Medicinal products can be provided by pharmaceutical companies either free of charge or sold to the Spanish National Health System. In the latter case, pharmaceutical companies may suggest a price for the purchase of the medicinal product. The decision on whether a medicinal product is supplied free of charge or at a purchase price depends on various factors, including, without limitation, the phase of development of the medicinal product or the need to gather additional information about its safety and efficacy.

Spain

Early Access and Compassionate Use

8. What tax treatment is applied to the company for the supply of medicinal products under early access and compassionate use programmes?

There is no specific tax treatment for the supply of medicinal products for compassionate use in Spain. Therefore, the tax treatment applicable to the supply medicinal products for compassionate use is the same tax treatment applicable to other medicines.

9. How can data obtained during an early access and compassionate use programme be used?

The decree does not set forth how to use data obtained during an early access or compassionate use programme. However, there was a public consultation process in order to improve certain aspects of the decree.

One of those aspects was precisely how to use the data obtained in order to generate evidence in those clinical trials where there is uncertainty and how to use the current technologies in order to increase a fluent communication between public administrations in order to generate knowledge associated with the use of medicines. However, no amendments to the decree have been approved yet in this regard.

10. Is there any provision for early access and compassionate use of medical devices?

Royal Decree 223/2004, on clinical trials with medicinal products, sets out the terms and conditions for compassionate use of medical devices. The decree fully replaced the regulation on compassionate use of medicines that was set out in the Royal Decree 223/2004.

However, the decree does not govern the compassionate use of medical devices.

Notwithstanding this, the AEMPS published in 2004 the Circular 7/2004 to clarify the provisions applicable to clinical trials of medical devices set forth in Royal Decree 223/2004, including, among others, the compassionate use of medical devices. This circular is still visible on AEMPS' website. According to certain Spanish doctrine, it is still applicable.

According to the circular, the following requirements apply to the supply of medical devices for compassionate use outside a clinical trial:

- AEMPS needs to authorise such compassionate use.
- The healthcare professional shall draft a report justifying the need to use the medical device.
- The manager body of the HCO needs to give its prior written approval to the use of the medical device for compassionate use.
- The patient (or their legal representative) will need to provide consent in writing for the compassionate use of the medical device.
- All medical devices shall comply with the relevant requirements of safety and health as required by the applicable law.

UK

Early Access and Compassionate Use

UK National Health Service (NHS) permits:

Compassionate use programme

- Per application of prescribers for their individual named patients
- As many authorisations as patients for whom a prescriber requests a compassionate use

At a price negotiated with the NHS

UK drugs agency **MHRA** can authorise:

Early Access to Medicine Scheme

- Per application of prescribers for their individual named patients, with the participation of the pharma company
- For all eligible patients

Free of charge

- For oncology products: possibilities for fundings with the Cancer Drugs Fund
- "Fast track": marketing authorisations and reimbursement dossiers strengthened with patients' data
- Can continue after marketing authorisation: until product admission to standard reimbursement

UK

Early Access and Compassionate Use

1. What are the laws or other mandatory rules that cover early access and compassionate use, if any?

In the UK compassionate use is governed by the Human Medicines Regulations 2012 (SI 2012/1916). Regulation 167 implemented article 5 of Directive 2001/83/EC in respect of the supply of unlicensed medicinal products to individual patients in the UK.

Regulation 46(7)(b) clarifies that the requirement for authorisation is subject to article 83 of the directive on compassionate use. In addition, the UK Early Access to Medicines Scheme (EAMS) was introduced in 2014 to allow physicians to prescribe medicines without marketing authorisation from the UK Medicines and Healthcare Products Regulatory Agency to patients with life-threatening conditions. The scheme was launched in 2014 and in 2022 was put onto a legislative footing via amendments to the 2012 Regulations.

2. What kind of patients or diseases can enter into an early access and compassionate use programme?

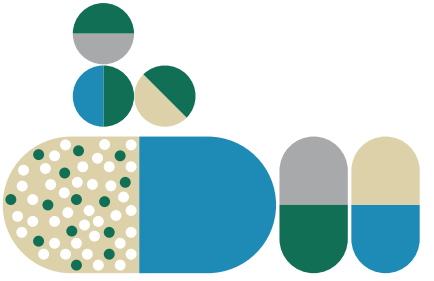
Under the regulations, the supply of an unlicensed product must be to fulfil the special clinical needs of an individual patient. Compassionate use is therefore only available where there is no pharmaceutically equivalent product already authorised and on the market in the UK.

EAMS applies to the supply of products to patients with a life threatening or seriously debilitating condition when there is a clear unmet medical need. The case study found on the NHS Early Access to Medicines Scheme website illustrates that an example product approved under EAMS was used to treat an advanced type of kidney cancer in routine clinical practice.

3. Which medicinal products can be made available in this way?

EAMS applies to medicines that have not been authorised for use by the medicines regulator – unlicensed medicines – where there is a clear unmet medical need

Medicinal products under EAMS will not have completed the full authorisation process and in general are supplied under EAMS for at least six months prior to marketing authorisation. MHRA guidance also recommends that if an off-label use of a product can meet the clinical needs of patients it should be used instead of an unlicensed product.



UK
Early Access and Compassionate Use

4. How do early access and compassionate use programmes work?

Medicines can be provided for compassionate use to NHS Trusts via three methods in the UK: the EAMS, manufacturer-led schemes and consultant-led schemes whereby consultants approach pharmaceutical companies and request for drugs for an individual patient with unmet needs.

In addition, prescribers can make individual patient requests for unlicensed medicines direct to the relevant person within the trust. Healthcare providers such as NHS Hospital Trusts and Clinical Commissioning Groups have their own policies on the commissioning and use of unlicensed medicines.

Under the regulations, an unlicensed medical product may only be supplied to patients if all of the following apply:

- There is an unsolicited order.
- The product is manufactured and assembled in accordance with the specification of a person who is a physician, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber registered in the UK.
- The product is for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient.
- The product is manufactured and supplied under specific conditions

A company provides the medicine free of charge to the NHS during the EAMS period which runs from the award of an EAMS positive scientific opinion up to commercial launch. (See here and here for information on the cost of the EAMS process).

In respect of EAMS, approval is a staged process.

- The pharmaceutical manufacturer applies for promising innovative medicine (PIM) designation when data from early stages in a clinical development indicates that the medical product fulfils the designation criteria. The MHRA will conduct a scientific meeting to consider the application.
- Provided a PIM designation is awarded, when the company has sufficient data to support patient access, they must make an EAMS scientific opinion application. These applications are reviewed by the independent Commission on Medicines (CHM). The EAMS scientific opinion considers the risks and benefits of the medicine by assessing the available quality, non-clinical and clinical data at the time of the application in accordance with the EAMS criteria.

A positive scientific opinion is valid for one year and is accompanied by a public assessment report published by the MHRA. This information supports the prescriber and patient in deciding on whether to use a medicine before its licence is approved.

UK
Early Access and Compassionate Use

5. Who can enter a patient within an early access and compassionate use programme?

Responsibility for deciding whether an individual patient has "special needs" within the meaning of the regulations which a licensed product cannot meet is a matter for the healthcare professional responsible for the patient's care. The requirement for a “special need” relates to the special clinical needs of the individual patient. It does not include reasons of cost, convenience or operational needs. The circumstances under which a healthcare professional can prescribe unlicensed medicinal products is subject to guidance from the General Medical Council most recently published in 2021.

6. Who is the issuer and the recipient of the application? What role does the national authority have in the process? What are the evaluation timelines?

In respect of the EAMS process, the application for EAMS approval is made by the pharmaceutical company manufacturer and submitted to the MHRA in accordance with the process outlined above.

Patient access to unlicensed medicines is facilitated by the relevant health care professionals. The prescriber is required to submit an approval form to the relevant entity or person as indicated in the relevant NHS Trust compassionate use guidance who will then review the application.

7. Can a medicinal product under the early access or compassionate use programmes be sold or must it be supplied for free?

Under EAMS, medicinal products are supplied free of charge. Under compassionate use programmes, pricing models vary.

8. What tax treatment is applied to the company for the supply of medicinal products under early access and compassionate use programmes?

There are incentives available for certain types of drugs such as orphan drugs (see guidance from the MHRA here). There are also general R&D tax break incentives for large companies (such as HMRC's Research and Development Expenditure Credit), which we understand could apply to a pharmaceutical company (see guidance here). Finally, there are grants in the UK that are available for specific drugs, which may extend to the provision of medicines for compassionate use. This would need to be considered on a case-by-case basis. We would recommend obtaining specialist tax advice on this point.

UK
Early Access and Compassionate Use

9. How can data obtained during an early access and compassionate use programme be used?

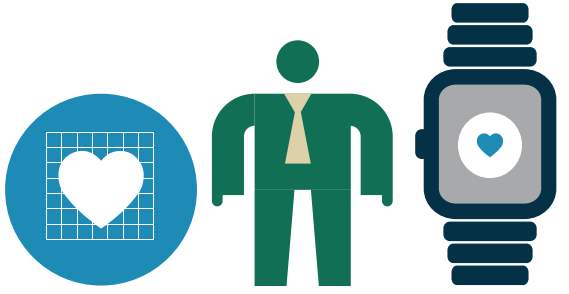
Data obtained within a compassionate use programme is primarily used for pharmacovigilance purposes. UK manufacturers and importers of unlicensed medicinal products are obliged to communicate all suspected adverse drug reactions to the MHRA. EAMS can generate real-world patient data in the NHS and can be collected without the need for authorisation under regulations applicable to clinical trials, subject requirements set out by the MHRA. The requirement to collect additional data and the nature and level of data to be collected will be agreed by all parties including clinicians and patients on a case-by-case basis.

10. Is there any provision for early access and compassionate use of medical devices?

Under Regulation 12(5) of the Medical Devices Regulations 2002, the MHRA may authorise manufacturers to supply a non-compliant device to protect a patient's health if there is no legitimate alternative available. Non-compliant devices are those which are not UKCA or CE marked. The same provisions can apply to custom-made devices. A manufacturer may be able to supply a non-compliant medical device for the treatment of a single-named patient in exceptional circumstances if:

- The clinician responsible for the patient's treatment supports the manufacturer's application.
- There is no alternative UKCA marked device available for this treatment.
- It can be demonstrated that mortality or morbidity is significantly reduced if the device is used compared to alternative compliant treatment.

Applications must be submitted by both the manufacturer and clinician to the MHRA. Applications are approved on a case-by-case basis for each time a device is used.



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