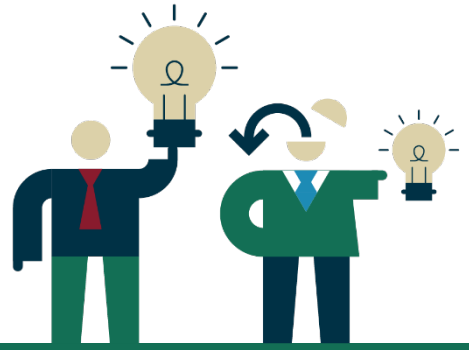
Compassionate use in Europe

The European Medicines Agency (EMA) defines "compassionate use" as *"the use of an unauthorised medicine outside a clinical study in individual patients under strictly controlled conditions"* or as *"a treatment option that allows the use of an unauthorised medicine"*.



Briefly, the European legal basis relating to compassionate use is provided for by:

- Article 5 of the Directive 2001/83/EC, which states that: *"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] medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his/her direct personal responsibility."*

- Article 83 of Regulation (EC) no. 726/2004, which provides, among other things, that: "*By way of exemption from Article 6 of Directive 2001/83/EC, Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and 3(2) of Regulation (EC) No 726/2004 available for compassionate use. "*

The implementation of compassionate use remains a responsibility of each Member State, which also need to consider the EMA Guideline on Compassionate Use of Medicinal Products. We are facing a substantial heterogeneity within the EU with regard to requirements and characteristics of compassionate use programmes, from which derives the purpose of this questionnaire.

Please click on the links below to find out each country's position on Compassionate use:

- Belgium
- France
- Germany
- Italy
- Spain
- United Kingdom

Compassionate use
Belgium

What are the laws (or other mandatory rules) that cover compassionate use in your country, if any?

In Belgium compassionate use is governed by the Act of 25 March 1964, or Medicines Act, and the Royal Decree of 25 April 2014 amending the Royal Decree of 14 December 2006 on medicinal products for human and veterinary use.

What kind of patients (or diseases) can enter into a compassionate use programme?

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 authorised medicinal product that is "reimbursed" and that is authorised and marketed (article 6, §1, 2° Medicines Act).

Which medicines can be made available in this way?

The Medicines Act refers to medicinal products belonging to the categories referred to in article 3(1) and (2) (that is, products covered by the centralised EU procedure)

Note that the medicinal product concerned must either be the subject of an application for a marketing authorisation by the centralised procedure (see article 6 of Regulation 726/2004) or must be undergoing clinical trials for the related indication.

In addition, the medical products used in compassionate use programmes need to be compliant with the requirements as described in article 107 of the decree:

- the label of the medication has to be conform with Annex 13 of Good Manufacturing Practice Guidelines, Volume 4, including the statement “Compassionate use – cannot be sold” in the 3 national languages (Dutch, French, German);
- individual exemptions on the language regimen can be requested.

How do compassionate use programmes work in your country?

Each compassionate use programme will have specific criteria according to which a patient can be included in the programme (see below for a practical overview of setting up a compassionate use programme). All patients that fulfil the inclusion criteria should have access to the programme unless objective and motivated limitations are stipulated in the programme.

Who can enter a patient within a compassionate use programme?

If a so-called compassionate use programme has been set up in accordance with the provisions of article 106 of the Royal Decree of December 14, 2006, any Belgian physician can submit an application to the responsible physician of the programme to have one or more of his patients included in that programme.

The treating physician will have to send his motivated request to the programme coordinator (in practice the pharmaceutical company). 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 disease, or a seriously debilitating disease, or a life-threatening disease, and that the disease cannot be treated satisfactorily using a medicinal product marketed in Belgium and which is authorised for treating this disease; the physician gives a description of the disease.
- He or she shall clearly and fully inform the patient concerned or his or her representative, pursuant to the Law 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.

Compassionate use
Belgium

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

Who is the issuer and the recipient, respectively, of the application?

The procedure to be followed in Belgium is set out in article 106 of the decree.

The application shall be submitted to the Minister or to his/her representative, in practice the Federal Agency for Medicines and Health Products (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 the patient(s) can be included in the programme;
- the person responsible for the programme;
- a standardised informed consent form for the patient which shall be submitted by the physician to the patients entering the programme (the FAMHP published templates for informed consent that could be adapted for compassionate use programmes);
- how the unused medicinal products shall be dealt with; and
- the information for registration of suspected unexpected serious adverse reactions (including the list of expected adverse reactions)

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

The FAMHP will contact the 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 data of the procedure is confirmed to the applicant by email within three days.

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

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 5 days later on the website of the FAMHP and are regularly reassessed.

How can data obtained during a compassionate use programme be used?

Data obtained within a compassionate use programme do not replace data required for the marketing authorisation procedure.

From a methodological point of view, clinical trials are the only means of obtaining reliable 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 clinical trials 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 inclusion/exclusion criteria, to follow-up the benefit-risk of a patient, pharmacovigilance data) could be used to enlarge the understanding of the treatment.

In any case, patients should always be considered for inclusion in clinical trials before being offered inclusion into a compassionate use programme.

Note that 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.

Compassionate use
Belgium

What tax treatment is applied to the company for the supply of medicines for compassionate use?

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

Did Covid-19 pandemic have an impact on compassionate use?

The FAMHP has received a number of urgent requests for compassionate use during the first and second peak of the pandemic. However, a compassionate use programme can be set up if a drug manufacturer wishes to make available a treatment for which it already has scientific results that allow it to demonstrate relative efficacy for a group of patients that cannot be treated satisfactorily. This procedure has also been developed in the context of the Covid-19 crisis.

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Compassionate use
France

What are the laws (or other mandatory rules) that cover compassionate use in your country, if any?

Compassionate use of pharmaceuticals in France is governed by the so-called “early access” regulatory framework set forth in article L.5121-12 of the French Code of Public Health (FCPH) and the compassionate use framework detailed in FCPH article L.5121-12-1.

France has always made this regime a priority to be attractive facilitating the access to innovative products for patients facing unmet therapeutic needs.

Formerly called the Authorisation for a Temporary Use (ATU) regime, it has been called the early access regime since the modifications adopted by the French Parliament through the Law of 14 Dec. 2020 for the funding of the French Health Insurance Programme in 2021.

France's prime minister then adopted the Decree of 30 June 2021 to implement the new early access and compassionate use regimes, and detail the various transitional time periods for switching from the former ATUs regime to these new regimes.

The main points to consider to differentiate the early access regime from the compassionate use regime are the related prior administrative authorisations that are required, as an exception to the general principle that no pharmaceutical product can be placed on the market without a marketing authorisation:

- Early access authorisations can be granted by the French High Authority for Health (HAS) through the application of a pharma company, for a group of patients.
- Compassionate use authorisations can be granted by the French Health Products Authority (ANSM), through the application of the physician who has his/her practice in a public hospital, for a named individual patient.

What kind of patients (or diseases) can enter into a compassionate use programme?

Both early access authorisation (EAA) and compassionate use authorisation (CUA) are focussed in scope on the diseases and the related available therapies.

Early access authorisation

EEAs can be granted for pharmaceutical products, on an exceptional basis and for specific therapeutic indications, 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 pharmaceutical product are highly presumed, on the basis of clinical studies results.
- the pharmaceutical product can be considered as innovative, in particular compared to other relevant therapies.
- An EEA can be granted by the HAS for a product to a pharma company only for one therapeutic indication which is:
  - not yet approved through the standard marketing authorisation (MA) of the product, provided that the company (applicant for the EEA) commits to submit an application for getting the therapeutic indication approved via the MA procedure within a period determined by the HAS (maximum two years from the granting of the EEA (the so-called pre-MA EEA); or
  - already approved under a standard MA, but not yet admitted to reimbursement through the French Health Insurance Programme, if the company (applicant for the EEA) commits to submit an application to get the therapeutic indication at stake admitted to reimbursement within one month from the granting of the MA (so-called post-MA EEA).

EEAs are granted for a period determined by the HAS (maximum 1 year) and can be renewed.

Compassionate use
France

Compassionate use authorisation (CUA)

CUAs can be granted, on an exceptional basis and for a specific therapeutic indication, for unapproved pharmaceutical 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 his/her 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 pharmaceutical product are highly presumed, on the basis of available clinical data.

CUAs are granted by the ANSM further to the application of a physician (prescriber) for a named patient only, for the use of an unapproved pharmaceutical product, or an approved product which is no longer commercialised if the therapeutic indication for which the product shall be used under the CUA is not approved by the Marketing Authorisation of such product.

Off-label Use

This is another pathway for compassionate use: the ANSM itself (or through the request of the MOH) can make the decision to pre-approve “compassionate prescriptions” of an approved pharmaceutical product, but for an unapproved therapeutic indication.

Who is the issuer and the recipient, respectively, of the application?

EAAs: The applicant is the company holding the rights for the product. The HAS is the competent authority for granting EEAs and the ANSM is involved for the validation of the protocol for the therapeutic use of the pharmaceutical product and for the collection of related health data (PTUD).

CUAs: The applicant is the doctor of a public hospital. The ANSM is the competent authority for granting CUAs. The pharma company holding the rights for the products is involved for the PTUD.

Off-label use: There is no application for prior authorisation per se, but a pre-approval decision made by the ANSM as its discretion (or per the request of the MOH) to secure compassionate prescriptions.

Which medicines can be made available in this way?

Please see the above section: pharmaceutical products intended only for the treatment of rare, serious or disabling diseases.

Who can enter a patient within a compassionate use programme?

- For products under EAAs: Unless otherwise determined in the PTUD, any doctor can prescribe the product for any eligible patient, but the products can be delivered only by pharmacies of public hospitals.
- For a product under a CUA: Only the public hospital doctor to whom the CUA has been granted can prescribe the product, and only for the named patient referred to by the CUA.
- For a pre-approved off-label use of a product: Unless determined otherwise in the ANSM decision, any qualified doctor could make a compassionate prescription for any eligible patient.

Compassionate use
France

How do compassionate use programmes work in your country?

EAAs are granted to pharma companies by the HAS together with a PTUD, which is drafted by the company in alignment with the ANSM.

In applications for pre-MA EAAs, the HAS decision must be based on the prior opinion of the ANSM. Given that no MA has yet been granted, it's indeed required that the ANSM confirms 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 data to collect under the PTUD pertain 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. The costs generated by the collection of such data must be incurred by the pharma company.

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 EEA*".

The EAA can be suspended or withdrawn by the HAS if:

- the conditions for their granted are no longer met (for example, marketing authorisation 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 marketing authorisation for the product, or its obligation to file an application to get the therapeutic indication admitted for reimbursement,
- there are deviations from the PTUD, safety issues with the product, negative opinion or refusal for the marketing authorisation.

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 (holder of the CUA) has his/her 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 marketing authorisation, but under a CUA, and be explained 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".

The CUAs can be suspended or withdrawn by the ANSM if the conditions for their granted are no longer met, or in the event of safety issues.

The off-label use pre-approved by the ANSM (compassionate prescription of a product in a therapeutic indication which is not approved through the MA of the product) lasts three years and can be renewed. Similarly to the CUAs, the ANSM can suspend or withdraw the conditions under with it has pre-approved an off-label use if the conditions are no longer met or in the event of safety issues.

How can data obtained during a compassionate use programme be used?

Data collected under PTUDs (both EAAs and CUAs) must be shared to the competent authorities (HAS and ANSM).

Such data could be used for supporting marketing authorisation files or "transparency files" (products dossiers for admission to reimbursement), but do not replace the standard clinical data required for the marketing authorisation procedures.

Compassionate use
France

What about the processing/collection of such personal data?

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

The relevant operator qualifying as 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,
- file to the CNIL a self-certification of compliance with, if applicable, a methodology of reference (MR), that is, guidelines in which the CNIL set forth requirements for securing privacy in the collection and processing of patients' health data: data controllers can self-certify that they comply with these requirements rather than applying for a prior authorisation.

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

Is there any provision for compassionate use of medical devices?

No, as of today in France, EAAs and CUAs are limited in scope to pharmaceutical products.

Must the products under compassionate use be supplied for free or can they be invoiced by pharma companies? Are the related costs covered by your National Health Insurance Programme?

A pharmaceutical product delivered under EAA, and also under a CUA if the product has not yet been admitted to reimbursement, can be invoiced at a price freely determined by pharma companies and the related cost is covered by the Health Insurance Programme.

However, as soon as the product (or the therapeutic indication) is admitted to reimbursement in France, its public price is determined by the French Pricing Agency (CEPS) and this public price is the basis for reimbursement by the National Health Insurance Programme. The difference between the price freely determined by the pharma company and automatically reimbursed by the Health Insurance programme during the EAA or the CUA, and the – lower – public price determined by the CEPS once the product is available to the general market after the final marketing authorisation and final admission to reimbursement, serves as a basis for calculating back-payments that the company must make directly to the French social security administration.

For a CUA granted for a product which has already been admitted to reimbursement, the compassionate use of the product in the – not yet admitted – therapeutic indication is covered by the Health Insurance Programme under the standard reimbursement regime (public price and reimbursement rate determined by the French authorities for the admission to reimbursement of the product for its other therapeutic indications).

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Compassionate use
Germany

What are the laws (or other mandatory rules) that cover compassionate use in your country, if any?

The main statutory rule in Germany for compassionate use is § 21 para. 2 No. 6 AMG ("Arzneimittelgesetz" = Medicines Act). This legal provision expressively refers to Art. 83 of Regulation (EG) No. 726/2004. It

While § 21 para. 2 No. 6 AMG regulates the conditions under which a compassionate use is permitted, the Federal Ministry of Health has issued a decree on the procedure. This decree is called "Arzneimittel-Härtefall-Verordnung" (AMHV, "Drug Hardship Decree"). It applies only to programmes intended to treat groups of patients.

What kind of patients (or diseases) can enter into a compassionate use programme?

Patients must have a disease that leads to severe disability or is life-threatening and cannot be satisfactorily treated with approved drugs.

Which medicines can be made available in this way?

§ 21 paragraph 2 No. 6 AMG refers to article 3 paragraph 1 and 2 of the Regulation (EG) No. 726/2004. Beyond the scope of the regulation, both centrally authorised medicinal products under the categories of article 3(1) and (2) of the regulation and nationally authorised medicinal products may be subject to compassionate use programmes.

Art. 3(1) of the regulation refers to the Annex 1, which identifies the following drugs:

- Medicinal products developed by means of one of the following biotechnological processes:
  - recombinant DNA technology,
  - controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
  - hybridoma and monoclonal antibody methods.
- Medicinal products for veterinary use intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.
- Medicinal products for human use containing a new active substance which, on the date of entry into force of this regulation, was not authorised in the community, for which the therapeutic indication is the treatment of any of the following diseases:-
  - acquired immune deficiency syndrome,
  - cancer,
  - neurodegenerative disorder,
  - diabetes,

and with effect from 20 May 2008

  - auto-immune diseases and other immune dysfunctions,
  - viral diseases.

After 20 May 2008, the European Commission, having consulted the European Medicines Agency, may present any appropriate proposal modifying this point and the European Council shall take a decision on that proposal by qualified majority.

- Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.
- Additionally, article 3 (2) provides for optional approval for drugs if: the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community; or the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community level.

Compassionate use
Germany

How do compassionate use programmes work in your country?

There is a significant difference between for programmes intended for the treatment of groups of patients and the treatment of an individual case.

- **Compassionate use programmes (hardship programmes) for a group of patients are governed by the above mentioned decree AMHV.** A compassionate use programme must be notified to the responsible higher federal authority by the responsible person before it begins. The German Federal Institute for Drugs and Medical Devices provides a guideline for the notification. The notification must provide various information, for example, the estimate of the number of patients. (The required information is enumerated by § 3 paragraph 2 AMHV.) Clinical trials have precedence over hardship programmes because the latter are not intended to be a substitute for clinical trials. The competent authority will confirm receipt of the notification within two weeks. Implementation of the hardship programme can begin as soon as the confirmed notification has been received and the authority has not objected. The programme ends after one year at the latest and must then be notified again. In any case, the responsible person shall submit a safety report after one year. The drug must be provided free of charge.
- **Individual cases are not covered by the legal regulations for compassionate use.** Drugs that have authorisation in another EU-country, but not in Germany, can be imported individually under § section 73 (3) AMG. A compassionate use treatment in individual cases with non-authorised drugs or by “off-label" use” would be measured by according to criminal law criteria. It must be examined individually in each specific case, to which extend the preconditions for a justifying state of emergency are met. A physician who performs an individual medical treatment bears the responsibility.

Who can enter a patient within a compassionate use programme?

To enter a programme, the responsible person has to make the above mentioned notification.

The wording of the AMHV does not lay down specific requirements regarding the legal personality of the responsible person. A responsible person can be either a natural or a legal person but can also be a civil law partnership (Gesellschaft burgerlichen Rechts). The responsible person can be the applicant for a central or national marketing authorisation or the sponsor of the authorised clinical trial. The responsible person bears the overall responsibility for the compassionate use programme. This includes initiation, organisation and financing of the compassionate use.

Who is the issuer and the recipient, respectively, of the application?

The competence of the competent higher federal authority is specified in § 77 AMG. In accordance with § 77 AMG, the competent higher federal authority shall be the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) unless the Paul Ehrlich Institut is responsible. In general, the competent higher federal authority that was or would be responsible for authorisation of a clinical trial with the medicinal product concerned is also responsible for the compassionate use programme.

How can data obtained during a compassionate use programme be used?

The authority makes available to the public information on compassionate use programmes notified to it. It therefore keeps an up-to-date list of the opinions adopted which is published on its website.

However, from a methodological point of view, only clinical trials are suitable for generating reliable data regarding the efficacy and safety of the drug. Compassionate use programmes are not a substitute for clinical trials. The data obtained in the context of a compassionate use programme cannot be compared in terms of validity with the informative value of findings from clinical trials in accordance with the standards of good clinical practice programme.

Compassionate use
Germany

Is there any provision for compassionate use of medical devices?

All legal regulations in Germany apply to drugs only.

The statutory rules for medical devices, currently the Medizinprodukterecht-Durchführungsgesetz (MPDG) to implement customs law), provide for the possibility of a special approval under the conditions of article 59(1) of Regulation (EU) 2017/745 (§ 7 MPDG).

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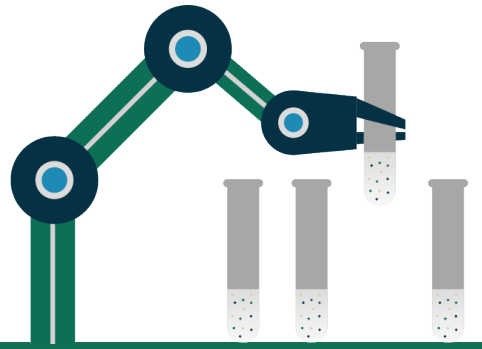

Compassionate use
Italy

What are the laws (or other mandatory rules) that cover compassionate use in your country, if any?

In Italy, compassionate use is governed by the Ministerial Decree of 7 September 2017. The decree repealed the Ministerial Decree of 8 May 2003, which is still in force with respect to compassionate use programmes activated before the entering into force of the decree on 2 December 2017.

What kind of patients (or diseases) can enter into a compassionate use programme?

Patients with serious diseases, rare diseases, rare 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.

In relation to the decree, these definitions apply:

- Rare diseases. A number of cases in a given population not exceeding the threshold of five cases per 10,000 people per year (and inclusion in one of the following reference lists: the EMA list of the National Centre for Rare Diseases, or the Istituto Superiore Sanita rare disease list.
- Rare tumours. These are tumours with an incidence of less than six cases per 100,000 per year.

Which medicines can be made available in this way?

Under article 1 of the decree, the following medicines can be made available through compassionate use programmes:

- Medicines that are not yet authorised and are under clinical trials and manufactured in pharmaceutical establishments or imported in accordance with the authorisation procedures and requirements provided for by the legislation in force (the proper "compassionate use", strictly speaking).
- Medicines with a marketing authorisation, but for indications other than those expressly authorised ("off label use").
- Medicines authorised but not yet available in the national territory ("foreign medicines").

Moreover, these medicines 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/two trials that are sufficient to make a favourable opinion on the efficacy and tolerability of the medicines requested for compassionate use.
- Be certified as being manufactured in accordance with good manufacturing practice.

In the case of rare diseases or rare tumours, at least phase-one clinical trials shall be available, and the latter shall also 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.

How do compassionate use programmes work in your country?

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

- An individual basis treatment (the so-called "uso nominale") that is "the compassionate use of medicines on an individual patient basis", not within a defined clinical protocol of compassionate use.
- A defined therapeutic programme. The latter is implemented by a pharmaceutical company, with previous approval by the Italian Medicines Agency (Agenzia Italiana del Farmaco (AIFA)). The company shall indicate the medicinal product which 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).

However, in normal circumstances, notification of the closure of the compassionate use programme must be submitted to AIFA at least 30 days before the effective closure date.

Compassionate use
Italy

Who can enter a patient within a compassionate use programme?

The request to enter a compassionate use programme shall be made by:

- the relevant health care professional (or group of health care professionals, 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 health care professional (single or group) for patients who attended a clinical trial which 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.

Who is the issuer and the recipient, respectively, of the application? What role does the national authority have in the process?

The application shall be submitted in advance by an 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 will then digitally transmit to AIFA its opinion, with all the relevant documentation, within three days from the adoption of the opinion, for informational purpose.

How can data obtained during a compassionate use programme be used?

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

Therefore, although safety data may be collected during the programmes, such programmes cannot replace clinical trials for investigational purposes. Compassionate use is not a substitute for properly conducted trials.

Is there any provision for compassionate use of medical devices?

Pursuant to article 11 of the Legislative Decree no. 46/1997, for the treatment of individual patients on a compassionate basis, in exceptional cases of necessity and urgency and within the procedures to be established by a ministerial decree, the Ministry of Health may authorise the use of medical devices that do not already have the CE certificate.

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 health care professional involved into the programme shall:

1. request the Ministry of Health for its use;
2. submit a specific report to the Ministry of Health and the relevant ethics committee (also with patient data);
3. wait for the ethics committee opinion and the Ministry of Health authorisation (within 30 days from the application).

Compassionate use
Italy

What tax treatment is applied to the company for the supply of medicines for compassionate use?

Under article 27 of the Decree Law no. 23/2020, converted into law with amendments by Law no. 40/2020, and the subsequent Italian Revenue Agency Circular no. 9/E and no. 26/E of 2020, the free supply of medicinal products for compassionate use is treated for VAT purposes as equivalent to their disposal. Thus, on the one hand, such 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.

There have been discussions about whether these tax measures will remain effective only during the Covid-19 pandemic.

Did Covid-19 pandemic have an impact on compassionate use?

AIFA slightly simplified the procedures for compassionate use programme for Covid-19 purposes.

In relation to therapeutic programmes, the requests for compassionate use should be sent, complete with a brief synopsis and protocol, to AIFA and the National Ethics Committee of the Spallanzani National Institute for Infectious Diseases. Data collection methods can also be sent after the first submission for evaluation purpose.

For individual basis treatment, the competence is of the local ethics committee.

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Compassionate use
Spain

What are the laws (or other mandatory rules) that cover compassionate use in your country, if any?

Article 24 of Spanish Act 1/2015, of July 24, on guarantees and rational use of medicines and health products, sets out 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.

What kind of patients (or diseases) can enter into a 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 a chronic or seriously debilitating disease or one that endangers the patient's life and cannot be treated satisfactorily with an authorised and marketed medicine.

Which medicines can be made available in this way?

Under article 2 of the decree, the following medicines can be made available through 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 ("off label use"); and
- medicines authorised in foreign countries but not yet available/authorised in Spain ("foreign medicines").

How do compassionate use programmes work in your country?

In Spain, we have the following compassionate use programmes:

- **Proper compassionate use programmes for medicines that are under clinical trials:** *Authorisation of individualised access:* An hospital or healthcare organisation ("HCO") shall, upon receipt of the approval of its manager body, request to the Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios, "AEMPS") the authorisation of a medicine that is under a clinical trial to be used on a case by case basis and outside such clinical trials. *Temporary authorisations:* Further, AEMPS may issue a temporary authorisation for the 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 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, obtaining his/her informed consent in accordance with the applicable law. AEMPS may develop recommendations for the use of the medicine when there is a potential 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/Regions or by HCOs designated by them.

Compassionate use
Spain

Procedure for access to unauthorised medicines in Spain through a protocol of use: AEMPS may develop protocols to set forth the conditions for use of a medicine not authorised in Spain when such medicine is expected to be used for a significant number of patients.

Who can enter a patient within a compassionate use programme?

The person or entity responsible to enter a patient within a compassionate use programme will depend on the type of compassionate use programme, as follows:

- Proper compassionate use programmes for medicines that are under clinical trials: the HCO, for individualised cases; and AEMPS, when the authorisation is given 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 professionals shall obtain the prior written informed consent of the patient; and follow the recommendations issued by AEMPS regarding the specific medicine, if any.
- Compassionate use programmes of foreign medicines: the health authorities of the Spanish Autonomous Communities/Regions or the HCOs designated by them.

Who is the issuer and the recipient, respectively, of the application? Please also specify which role does the relevant National Authority have in the process.

As stated in our previous answer above, the issuer and the recipient may depend on the type of compassionate use:

- 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 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 of 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/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 use of a medicine not authorised in Spain when this medicine is expected to be for a significant number of patients.

How can data obtained during a compassionate use programme be used?

The decree does not set forth how to use data obtained during a compassionate use programme.

However, there was a public consultation process in order to improve certain aspects of the decree.

One of those aspects is 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.

The consultation process terminated in January 2021. However, no amendments to the decree have been discussed or approved yet.

Compassionate use
Spain

Is there any provision for compassionate use of medical devices?

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

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

Notwithstanding the above, 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 available 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 shall give its prior written approval to the use of the medical device for compassionate use.
- The patient (or its legal representative) shall provide his/her 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.

What tax treatment is applied to the company for the supply of medicines for compassionate use?

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

Did Covid-19 pandemic have an impact on compassionate use?

During the beginning of the Covid-19 pandemic, AEMPS published a resolution regarding the available treatments for the management of SARS-CoV-2 respiratory infection. In some cases, the treatment for patients with Covid-19 infection could be accessed, mainly through compassionate use programmes, since there were no approved treatments for such infection. Furthermore, AEMPS provided access to compassionate programmes to the hospitals.

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Compassionate use
United Kingdom

What are the laws (or other mandatory rules) that cover compassionate use in your country, if any?

In the UK compassionate use is governed by the Human Medicines Regulations 2012 (SI 2012/1916) ("Regulations"). Regulation 167 implements 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 Art. 83 of the Directive on compassionate use. In addition, the UK Early Access to Medicines Scheme (EAMS) was introduced in 2014 to allow doctors 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 runs in parallel with the existing UK licensing procedures contained in the Human Medicines Regulations 2012.

There is currently no UK legislation that specifically covers EAMS. However, the UK government has conducted a consultation on proposed legislative changes to the Human Medicines Regulations 2012 to provide a specific statutory basis for the delivery of the Early Access to Medicines Scheme (EAMS). The proposed changes can be found here.

Which medicines can be made available in this way?

EAMS applies to:

- medicines that have not been authorised for use by the medicines regulator ('unlicensed medicines') and;
- medicines that have medicines regulatory approval but are used in a different condition or patient group that does not have marketing authorisation ('off label medicines').

The EAMS is primarily aimed at medicines that have completed Phase III trials but may be applied to completed Phase II trials in exceptional circumstances.

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.

Note that this may change following the results of the consultation, once EAMS is regulated under the regulations.

What kind of patients (or diseases) can enter into a com-passionate 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.

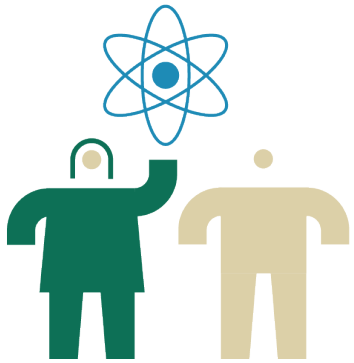
EAMS applies to the supply of products to patients with a life threatening or seriously debilitating condition when there is a clear unmet medical need. The case study found on the NHS Early Access to Medicines Scheme website illustrates that one product approved under EAMS is used to treat an advanced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

Compassionate use
United Kingdom

How do compassionate use programmes work in your country?

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 (as per the regulations). Healthcare providers such as NHS Hospital Trusts and Clinical Commissioning Groups have their own policies on the commissioning and use of unlicensed medicines. For example, an NHS Trust in London has its own approval policy in place for the 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 doctor, 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 (see Sections 3 to10).

A company provides the medicine free of charge to the NHS during the EAMS period which is defined as after the award of an EAMS positive scientific opinion and up to the granting of the marketing authorisation. (See here for information on the cost of the EAMS process).

In respect of EAMS, approval is a two-step 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.

Compassionate use
United Kingdom

Who can enter a patient within a 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 2013.

Who is the issuer and the recipient, respectively, of the application?

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/person as indicated in the relevant NHS Trust compassionate use guidance who will then review the application.

Is there any provision for 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/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 manufacturers application;
- there is no alternative UKCA marked device available for this treatment; and
- 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.

How can data obtained during a 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 (regulation 170).

EAMS can generate real world patient data in the NHS. 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.

How data is collected, stored and used under EAMS is one of the areas which has been looked at under the EAMS consultation which closed in September 2021.

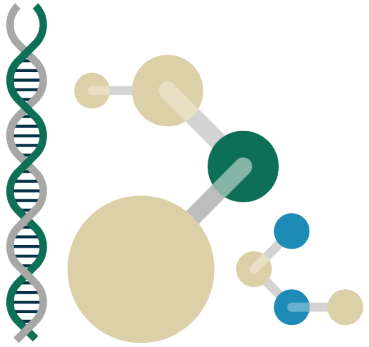
Compassionate use
United Kingdom

What tax treatment is applied to the company for the supply of medicines for compassionate use?

There are tax breaks 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 (RDEC)), 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.

Did Covid-19 pandemic have an impact on compassionate use?

We are not aware of specific flexibilities introduced due to Covid-19. However, we will need to wait and see the results of the EAMS consultation.



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