

Accessing unapproved drugs

Information Sheet H

The purpose of this information sheet is to provide material on how you may be able to access drugs that don't yet have regulatory approval, assuming they will be approved and available at some point. It also aims to help you understand terms such as orphan drug status, 'EAMS', off-label, or named patient basis, and how these might be relevant in the process of drug approval.

There are many drugs for the treatment of MND that are currently being tested in clinical trials. This information sheet is not designed to address these, but information on these can be obtained through the **www.clinicaltrials.gov** website, which includes clinical trials across the world, or the **NIHR Trials Gateway** (for UK trials).

The information in this document is based on UK laws and practice standards, unless otherwise stated.

The content is split into the following sections:

- 1: Clinical trials**
- 2: Orphan drug status**
- 3: Marketing approval of a drug**
- 4: Early (conditional) licensing**
- 5: Other ways to access unapproved drugs**
- 6: Practical examples**
- 7: How do I find out more?**

Disclaimer: *Please note that information provided in this information sheet is based on a review of the currently available literature. This information sheet was written by MND Association staff who are not clinicians, so any information provided in this sheet should not be considered clinical advice. You should always discuss potential treatments with your clinician.*



This symbol is used to highlight **our other publications**. To find out how to access these, see *Further information* at the end of this sheet.

What do the words and abbreviations mean?

Committee for Medicinal Products for Human Use (CHMP):	Committee of the European Medicines Agency (EMA) responsible for human medicines.
Conditional licence:	Temporary licence that may be awarded by the EMA to drugs that have not yet been granted a full licence.
Early Access to Medicines Scheme (EAMS):	The UK scheme for accessing medicines that have not yet been licensed.
European Medicines Agency (EMA):	The European Union (EU) agency that evaluates medicinal products and grants marketing approval.
Expanded access:	The USA scheme for accessing medicines that have not yet been licensed (also known as 'compassionate use').
Food and Drug Administration (FDA):	The USA agency that evaluates medicinal products and grants marketing approval.
General Medical Council (GMC):	The official register of medical practitioners in the UK.
Marketing authorisation:	Licence awarded to a drug after it has been proven to be safe and beneficial.
Medicines and Healthcare products Regulatory Agency (MHRA):	The UK agency that evaluates medicinal products and grants marketing approval.
National Institute for Health and Care Excellence (NICE):	The UK public body that publishes evidence-based guidance on effective ways to prevent, diagnose and treat ill health.
Off-label:	The use of a licensed drug in a different way than stated in its licence (e.g., for a different condition)
Open label:	A phase at the end of a clinical trial when all participants are offered a trial drug.
Orphan disease:	A chronic or life-threatening disease that is considered a 'rare' disease.
Orphan drug status:	A status given to a drug to provide guidance and support throughout its development process.
Placebo:	An inactive compound ('dummy drug') given to half of participants in most clinical trials.
Promising Innovative Medicine:	First stage of the UK EAMS approval process.
Scientific Opinion:	Second/final stage of the UK EAMS approval process.

1: Clinical trials

Before a drug is made generally available to patients it needs to undergo a series of tests known as clinical trials. This is to make sure that the drug is safe to give to people, and more specifically to those with the condition or disease the drug has been designed for. The other purpose of clinical trials is to test whether the drug has a beneficial effect and look at the best dosage and the way/route by which to deliver it (e.g., injection, pill).

If the last stage of a clinical trial is successful, it can take a long time before the drug is available on the NHS or in the pharmacy. This information sheet aims to explain how people may be able to access drugs in this period and provide accurate information on the drug approval process.

Open label phase of clinical trial

In most clinical trials, only some people receive the drug under investigation, while others receive a dummy drug (placebo) – this is to observe the real effects of the drug. Occasionally, at the end of the study period, participants from both groups have the opportunity to take the drug. This is known as an ‘open label’ phase of the study, and often runs while the results of the study are being analysed or while the study is still ongoing (as the recruitment period can be over a few months, not everyone will start the trial on the same day). The open label phase can sometimes be planned from the outset of the study, while at other times the researchers decide to add it on as the study progresses. Only individuals in the original trial can enter the open label phase.

If a drug is made available in an open label phase of a clinical trial, it does not mean that it has been shown to be of benefit for people living with the condition, but rather it gives a chance to all participants to take the drug.



For further information about how clinical trials are conducted, see: Information sheet D – *Clinical trials*.

2: Orphan drug status

The development of a drug is a big investment for pharmaceutical and biotechnology companies, typically involving many years of research and development (often greater than 10 years) before clinical trials can even begin. Many compounds that have been developed for years might never even make it to the market.

Traditionally, there is likely to be a better chance for a company to recoup these costs and make a profit if the drug could be used to treat a common condition that affects a large proportion of people, such as a drug for the treatment of heart disease or cancer. It is much less attractive for companies to develop a drug for a rare disease where the

market and potential profits are smaller. To address this, the drug licensing authorities in Europe (European Medicines Agency; EMA) and the USA (The Food and Drug Administration; FDA) have an 'orphan status' scheme in place.

An orphan status can be designated to drugs intended for treatment of chronic or life-threatening diseases that are considered a 'rare' disease. This applies to diseases where the prevalence is no more than 5 in 10,000 people (or where, in the USA, it affects less than 200,000 people) and for which there are no satisfactory treatments. The company developing the drug must also be unlikely to recoup the costs of the development by marketing it.

MND/ALS meets the criteria of an orphan disease in both Europe (~1 in 10,000 people at any one time) and USA (~20,000 people currently living with MND/ALS).

Advantages of orphan drug status

If a drug is given orphan drug status, **it does not mean that it has been shown to be of benefit to people living with the specific condition** (this has to be established through clinical trials).

Companies must apply for orphan drug status for the drugs they are developing (as this doesn't happen automatically), while they are still being developed in the lab. When a drug is given orphan drug status, support is provided at various stages along the drug development process; this includes assistance with the research and development stage of the drug, and financial and regulatory matters - effectively 'fast tracking' a drug through the process. Orphan drug status can be particularly helpful for smaller companies or academic research groups who typically have less resources and experience than large pharmaceutical companies.

Another important advantage is that of market exclusivity – in other words, other companies won't be able to make or sell the same product for up to 10 years after the drug has been licensed. (Most new drugs are patented, which also offers market exclusivity. Orphan drug status however offers a longer period of exclusivity than patents.)

3: Marketing approval of a drug

When a drug has been proven to be safe and demonstrated to have a beneficial effect through rigorous clinical trials, the next step for the pharmaceutical company developing the drug is to apply to an appropriate regulatory authority to approve it. This is known as '**licensing**', '**marketing approval**', or '**marketing authorisation**'.

Each regulating authority will have different criteria for approving drugs. This may explain why a drug is available to treat MND in one country, but not in another. Each drug licence specifies which condition it can be used for, who it is aimed at, the type

of delivery, and dosage. One drug can therefore have multiple licences for different conditions.

In the UK, drugs are licensed either a) directly through the **Medicines and Healthcare products Regulatory Authority (MHRA)**, or b) via the **Committee for Medicinal Products for Human Use (CHMP)** of the **European Medicines Agency (EMA)**, a central European agency, where licences are then adopted by the MHRA.

Most regulating authorities have a two-tier licensing system:

- 1) The first tier is to give a full licence or marketing authorisation, when all stages of the clinical trial have been completed and a beneficial effect of the drug was found.
- 2) The second tier is a system for specific groups of patients to be able to access a drug at an early stage, when the clinical trials for full approval aren't complete; examples of this are 'conditional licencing', or 'early access' schemes. Each regulatory authority has different rules that need to be met before a company can apply for one of these early licences.

4: Early (conditional) licensing

EMA conditional approval – EU approval

The EMA licenses drugs across the whole of the EU, where the licensing decision is valid across member states. They can either give a drug a full licence, or a conditional licence if a drug is still at an earlier stage of development (e.g., Phase II/III trial). When a drug is being developed for a condition for which no drugs are available, or the current treatments have a limited effect, the EMA may give a short-term licence while the studies for a full licence are still underway. This is known as a **conditional approval**, or a **conditional licence**. It lasts for 12 months (which can be renewed) and is only granted if the company commits to finishing the studies required for full approval.

The MHRA regulates drug use in the UK, and adopts decisions made by the EMA. It can also grant licences in its own right; that is, it can grant a licence within the UK without an approval for the rest of the EU. Aside from a full licence, the MHRA can issue an approval within the Early Access to Medicines Scheme (EAMS).

Early Access to Medicines Scheme (EAMS) – UK approval

This UK scheme was introduced by the MHRA to make it possible for promising unlicensed drugs or treatments to be made available to patients sooner, before the marketing approval stage. These medicines may be part of ongoing research, so there is a chance the medication could have unknown side effects or may not be effective. The full results from the Phase III trial of the medicine may also not be known at this stage.

The scheme requires drug companies with promising compounds to apply for a two-stage process, during which the drug must be designated as a **'Promising Innovative Medicine'** based on available preclinical and clinical data, and obtain **'Scientific Opinion'** on the *risk:benefit* balance based mainly on Phase III data (or Phase II in exceptional circumstances).

The positive/negative decision is often given within 90 days. If the opinion is negative, it will not be published and the applicant cannot appeal. If the opinion is positive, the drug company must pay the costs of making the drug available.

Throughout the whole process, the MHRA keeps the National Institute for Health and Care Excellence (NICE) informed of the applications, with the aim to make approved drugs available on the NHS across the UK more quickly after they are licensed.

Since its launch in 2014, the EAMS system has awarded 20 licences, the majority of which have been for cancer treatments, and currently **none for MND**.

It is important to note that the EMA's conditional licence and the UK Early Access to Medicine Scheme work differently, and use different criteria to agree these early licences. It cannot be assumed that a drug with the EMA's conditional licence is also part of the EAMS and vice versa.

The role of NICE in drug approval

Licensing a drug doesn't take into account the cost of the drug, its economic impact, or when or how it should be made available. These are taken into consideration by other organisations, such as NICE in England.

NICE is an independent body with an aim to improve outcomes for people using the NHS and other public health and social care services.

One of its roles is to assess new and existing treatments on clinical efficacy and cost effectiveness. This is to ensure that all NHS patients have equal access to the most clinically- and cost-effective treatments that are viable.

Guidance and assessments from NICE are directly applicable in England, and are also routinely adopted in Wales and Northern Ireland.

Worldwide licensing

USA

The US Food and Drug Administration (FDA) has a scheme called 'Expanded access' (or 'Compassionate use') that approves investigational drugs before they are approved for marketing in the USA. This includes approval for individuals or patient groups.

Find out more about the scheme on the FDA website (find the link in the 'How do I find out more?' section).

In May 2018, a new 'Right to try' legislation came into effect across the US, allowing people with terminal diseases to obtain drugs tested in Phase I (i.e., establishing their safety, but not efficacy) directly through the pharma company via a physician. As this law doesn't require application to the FDA, the information and knowledge gained from previous studies and clinical trials might not be available to individuals.

Europe

Many European countries have their own, country-specific rules for allowing people to access drugs before enough data have been collected to give full approval. Each regulatory body has its own rules for deciding what makes a drug eligible for these schemes, and the criteria for whether or not early access is granted.

For more information on early access to medicines in the individual countries that fall within the EMA, please contact the regulators via a directory on the EMA website (find the link in the 'How do I find out more?' section).

5: Other ways to access unapproved drugs

Named patient basis (also known as 'specials')

In addition to the formal early access schemes described above, people can also ask their doctor to request a drug, not currently licensed for their condition in the UK, specifically for them. However, getting named patient approval ('specials') is a lengthy and complex process involving a number of different steps at different levels.

MHRA guidance

The MHRA requires all drugs to have approval before they can be used in the UK. However, there are circumstances where this approval is not required, and the MHRA will allow the use of unlicensed drugs via the named patient basis.

This would require agreement from a doctor looking after the individual to request a supply of the drug from the drug company. The doctor would need to seek local NHS permissions to be able to prescribe the drug. The costs of the drug and delivery would need to be met. The use of the drug must be supervised by a pharmacist (either in a hospital or community-based pharmacy).

For a drug in such an early stage of development it is unlikely that all agreements and permissions would be met.

The decision of ordering the drug falls on the individual's doctor, which is a big responsibility to have; the physician is responsible for any harm to the patient due to any unknown side effects. Physicians may want to seek advice from their colleagues and also from the General Medical Council (GMC) when making this decision.

Find out more about named patient basis drugs on the MHRA website. For guidance for doctors who consider prescribing a drug on a named patient basis, see the GMC website (find the link in the 'How do I find out more?' section).

Practical considerations

If a doctor agrees to order a drug on a named patient basis there are some practical issues that need to be overcome. Namely, the agreement of their employing NHS Trust, the supervision of a pharmacist (as required by the MHRA), and working out the financial implications, including how the costs of the drug will be met. The costs may be borne by the drug company, the local NHS trust or local commissioners. In some circumstances a patient may seek to fund the costs themselves.

Local NHS permission and arrangements for pharmacist supervision may take a number of routes including discussions at local drugs and therapeutics committees, area prescribing committees and/or with the chief pharmacist.

If the drug is manufactured outside the UK, its importation is subject to a special licence provided to the importer. The MHRA also needs to be notified at least 28 days before the import, and should be supplied with information about the drug.

Off-label drugs

Ordering a drug on a named patient basis is different from off-label use. Off-label treatment is the use of a licensed drug in a different way than stated in its licence; most often for a condition it was not originally licensed for. Because these drugs have already undergone safety trials, doctors may prescribe them if they are convinced that it will help their patient.

6: Practical examples

This section will put the information above into practice by including specific or theoretical examples of the different stages of drug approval.

Scenario 1: Riluzole

Riluzole is an example of the typical process of drug approval. It underwent clinical trials for ALS/MND in the early 1990s, followed by marketing approval in the UK in 1996. In 2001 it was recommended by NICE to be used across the NHS.

Riluzole is currently the only drug licensed to treat MND in the UK. It has the potential to increase survival by 2-4 months after 12-18 months of treatment.

UK access: Fully licensed, all people living with MND should have access to this drug.



For further information about riluzole, see: Information sheet 5A – *Riluzole*.

Scenario 2: Edaravone

Edaravone's initial purpose was to help recovery from a stroke. However, after clinical trials in 2011 in Japan, it was licensed to treat MND in 2015 in Japan and in 2017 in the USA and is now also licensed for use in South Korea, China and Canada. The pharma company applied for marketing authorisation with the EMA but in May 2019 informed the CHMP that it was withdrawing its application for marketing authorisation for edaravone. At that time, the CHMP was of the opinion that they would not be authorising edaravone for the treatment of MND as they felt that the lack of evidence of effectiveness meant that the benefits of taking the drug did not outweigh the risks. The pharma company stated this as the reason for the withdrawal.

Edaravone gained orphan drug status in the EU in 2016.

UK access: Currently, the only way to access edaravone is on a named patient basis.

Scenario 3: Orphan drug compound

There have been some studies conducted in laboratory models of MND showing that a specific drug may have a beneficial effect for MND. The company/research group have applied for orphan medicinal status for the drug to assist with its further development. This does not mean that there is evidence that the drug has a beneficial effect.

UK access: This drug can be accessed on a named patient basis, or, if already licensed in the UK for a different condition, as an off-label treatment via a physician.

Scenario 4: Early stage clinical trial

Results from Phase III (or exceptionally Phase II) of a drug trial were announced, and the drug has been shown to be safe with at least some sign of beneficial effects. The pharma company applies for conditional licence under the EAMS which is accepted. The drug is made available for 12 months during which it is provided by the pharma company free of charge via the NHS.

During the EAMS period, the drug is still being developed and the pharma company may apply for full marketing authorisation.

UK access: The drug can be prescribed by a physician during the EAMS period.

4: How do I find out more?

Useful organisations

We do not necessarily endorse any of the following organisations but have included them to help you begin your search for further information.

The contact details are correct at the time of publishing but may change between revisions. If you need help to find an organisation, contact the Research Development Team (see *Further information* at the end of this sheet for details).

Clinical trials database

Web-based resource to provide easy access to information on clinical trials worldwide.

Website: www.clinicaltrials.gov

European Medicines Agency (EMA)

The European Union (EU) agency that evaluates medicinal products and grants marketing approval.

Email: via their website contact page

Website: www.ema.europa.eu

Food and Drug Administration (FDA)

The US agency that evaluates medicinal products and grants marketing approval.

Email: via their website contact page

Website: www.fda.gov

General Medical Council (GMC)

The official register of medical practitioners in the UK.

Website: www.gmc-uk.org

Medicines and Healthcare products Regulatory Agency (MHRA)

The UK agency that evaluates medicinal products and grants marketing approval.

Address: 10 South Collonade, Canary Wharf, London, E14 4PU

Email: info@mhra.gov.uk

Website: www.gov.uk/mhra

National Institute for Health and Care Excellence (NICE)

The UK public body that publishes evidence-based guidance on effective ways to prevent, diagnose and treat ill health.

Address: 10 Spring Gardens, London, SW1A 2BU

Email: nice@nice.org.uk

Website: www.nice.org.uk

NIHR Trials Gateway

The UK's National institute for Health Research (NIHR) website aims to help people make informed choices about taking part in clinical trials.

Website: www.ukctg.nihr.ac.uk

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Further information

You may find these information sheets from the MND Association helpful:

D – *Clinical trials*

5A – *Riluzole*

We also provide the following guides:

Living with motor neurone disease – our main guide to help you manage the impact of the disease

Caring and MND: support for you – comprehensive information for unpaid or family carers, who support someone living with MND

Caring and MND: quick guide – the summary version of our information for carers

You can download most of our publications from our website at www.mndassociation.org/publications or order in print from the MND Connect helpline, who can provide further information and support.

MND Connect can also help locate external services and providers, and introduce you to our available services, including your local branch, group, Association visitor or service development manager.



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MND Association website and online forum

Website: www.mndassociation.org

Online forum: forum.mndassociation.org or through the website

We welcome your views

Your feedback is really important to us, as it helps improve our information for the benefit of people living with MND and those who care for them. If you would like to provide feedback on any of our information sheets, you can access an online form at: www.surveymonkey.co.uk/r/infosheets_research

You can request a paper version of the form or provide direct feedback by email: research@mndassociation.org.