# Macimorelin for diagnosing growth hormone deficiency

Medtech innovation briefing
Published: 28 March 2023

www.nice.org.uk/guidance/mib320

## Overview

NICE has developed a medtech innovation briefing (MIB) on macimorelin for diagnosing growth hormone deficiency.

The information provided includes a description of the technology, how it's used and its potential role in the treatment pathway. A MIB also includes a review of relevant published evidence and the likely costs of using the technologies, but they are not NICE guidance and do not make any recommendations on the value of using the technologies.

## Summary

- The **technology** described in this briefing is macimorelin. It is used for diagnosing growth hormone deficiency (GHD) in adults.
- The **innovative aspects** are that it is the only oral growth hormone stimulation test and does not rely on inducing hypoglycaemia to provide a growth hormone response.

- The intended **place in therapy** would be as an alternative to all currently available GHD tests, including the insulin tolerance test in adults with GHD.
- The **main points from the evidence** summarised in this briefing are from 2 studies (1 multicentre randomised crossover trial with a subgroup post-hoc analysis and 1 multicentre open-label study), which include a total of 237 people. They show that macimorelin is an effective and safe test for diagnosing adult growth hormone deficiency (AGHD) with accuracy comparable with other tests, including the insulin tolerance test.
- **Key uncertainties** around the evidence are that there is only 1 randomised crossover trial, with a secondary analysis, and 1 study that had to be altered because the comparator was discontinued. Only 1 NHS trust was included in the randomised crossover trial, which was done in the US and across 25 sites in Europe.
- **Experts advised** that macimorelin is less invasive than other GHD tests because it is taken orally, needs fewer blood samples, has a shorter procedure time, can be done in an outpatient setting and has fewer side effects. It can be used when the insulin tolerance test is contraindicated. They noted that further research is needed on its tolerability, the impact of body mass index on its effectiveness and its use when the insulin tolerance test is contraindicated.
- The **cost** of macimorelin is about £421 per test (excluding VAT). The cost of standard care is between £439 and £470 per test.

# The technology

Macimorelin (Aeterna Zentaris) is a medicine that stimulates the release of growth hormone into the blood. It is used to test the body's ability to produce growth hormone and therefore diagnose growth hormone deficiency (GHD). It is not used as a treatment for GHD. It is available as granules (60 mg) that are dissolved in water and taken orally. It should be taken once, and the recommended dose is 0.5 mg per kg body weight. Blood samples are then taken at 45 minutes, 60 minutes and 90 minutes to see how much growth hormone the body produced.

## Innovations

The company claims that macimorelin is the only oral growth hormone stimulation test for

diagnosing adult growth hormone deficiency (AGHD). It claims that its mode of action is innovative because it works directly at the pituitary gland and, unlike the insulin tolerance and glucagon tests, it does not rely on inducing hypoglycaemia to provide a growth hormone response. The company also claims that macimorelin is quick and easy to administer. It takes about 90 minutes with 3 blood draws compared with 120 to 180 minutes and 7 blood draws for the insulin tolerance test and 240 to 300 minutes and 7 to 9 blood draws for the glucagon test. The company claims it has fewer contraindications than the insulin tolerance test, which has significant contraindications, so it could potentially reduce barriers to testing and improve access to treatment.

# Current care pathway

Several tests are available to diagnose GHD. The gold standard is the insulin tolerance test. A general definition of severe GHD in adults is a peak concentration of less than 9 mU/litre (3 ng/mL) in response to insulin-induced hypoglycaemia. When the insulin tolerance test is contraindicated, other tests can be used, such as response to growth hormone-releasing hormone (GHRH), arginine or glucagon.

The following publication has been identified as relevant to this care pathway:

- NICE technology appraisal guidance on human growth hormone (somatropin) in adults with growth hormone deficiency (TA64).

# Population, setting and intended user

Macimorelin is used for adults with GHD. The Society for Endocrinology estimates that the prevalence of adult-onset GHD is about 1 in 10,000 of the adult UK population (see NICE's technology appraisal guidance TA64 [2003]). This equates to about 5,600 adults with adult-onset GHD in England.

The technology is intended for use in secondary or tertiary care. Macimorelin will likely be used by endocrinology clinicians with experience in diagnosing GHD. Usually, the test will be administered by an endocrinology nurse specialist.

The company states that the test is easy to administer and staff do not need additional training, but, if needed, self-directed training is available online and consists of web access to a summary of product characteristics, a 'how to use' leaflet, a simple video

explaining the steps and a 'how to use' protocol developed by UK endocrinology clinicians. This is included in the cost of the technology.

# Costs

## Technology costs

The NHS list price for macimorelin is £300. The company states that the full procedural cost, including clinician time to administer and supervise the test (2 hours of nurse time), is £421.30 per test (excluding VAT).

## Costs of standard care

The insulin used in the insulin tolerance test costs £3.96. The full procedural costs are £438.91 per test (including 4 hours of nurse and 1 hour of doctor time). The alternative test, the GHRH-arginine test, has a cost of £89.48 for both tests and a total procedure cost (including 4 hours of nurse and 1 hour of doctor time) of £469.60 per test (excluding VAT).

# Resource consequences

The company states that macimorelin was launched for use in the NHS in May 2022 but is currently not used. The company is engaging with key secondary and tertiary units to add macimorelin to their formulary list.

The company claims that the testing procedure time with macimorelin is considerably shorter, lasting 90 minutes compared with 2 to 4 hours or more for other GHD tests. It claims this will reduce medical resource costs and save clinician time. The company also claims that macimorelin has fewer contraindications and a more favourable safety profile compared with the insulin tolerance test and does not involve inducing hypoglycaemia. It claims that the total budget impact of macimorelin is substantially lower than standard care. This is supported by a budget impact analysis published as a conference abstract, but limited detail is available (English et al. 2022).

The company states that adopting macimorelin in clinical practice does not need any changes to facilities or infrastructure.

# Regulatory information

Macimorelin (also known as Ghryvelin) received marketing authorisation from the European Medicines Agency for diagnosing adult growth hormone deficiency in January 2019 (EU/1/18/1337/001).

# Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Most cases of adult growth hormone deficiency are because of damage to the pituitary gland caused by a tumour or by the treatment of a tumour. The cause of these brain tumours is unknown, but people are more likely to develop them if they are aged 50 or over, have a family history of brain tumours, have had radiotherapy or if they have a genetic condition. Age and disability are protected characteristics under the Equality Act 2010.

# Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement for medtech innovation briefings. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

## Published evidence

Three studies are summarised in this briefing, including 164 people with confirmed adult growth hormone deficiency (AGHD) or a high, intermediate or low likelihood of AGHD and 73 matched controls. The post-hoc analysis included 41 people with a high likelihood of AGHD and 25 healthy matched controls, both included in the number above.

The studies include 1 randomised crossover trial with a post-hoc analysis of a subgroup from this trial and 1 multicentre open-label study (initially planned as a crossover study).

There is a phase 1 randomised controlled trial evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of macimorelin in healthy adults (Klaus et al. 2020) that is not summarised below.

The clinical evidence and its strengths and limitations are summarised in the overall assessment of the evidence.

# Overall assessment of the evidence

The evidence ranges from low to high methodological quality, and most studies had small sample sizes. The phase 3 randomised crossover trial was done in the US and 25 sites across Europe, which included 1 NHS trust. The studies suggest that macimorelin is an effective and safe test for diagnosing AGHD and its accuracy is comparable with alternative tests, including the insulin tolerance test. Further research is needed comparing macimorelin with alternative tests in the UK.

## Garcia et al. (2018)

### Study size, design and location

A multicentre, phase 3, open-label randomised two-way crossover trial in 114 people with high, intermediate and low likelihood of AGHD and 25 healthy matched controls in the US and 25 sites across Europe.

### Intervention and comparator

Macimorelin compared with the insulin tolerance test.

### Key outcomes

In total, 139 people were included in the analysis. Of these, 38 were included in the high likelihood group (group A), 37 in the intermediate group (group B) and 39 in the low likelihood group (group C). Group D consisted of 25 healthy matched controls. Using the prespecified growth hormone cut-off levels of 2.8 ng/mL for macimorelin and 5.1 ng/mL for the insulin tolerance test, the negative agreement was 95.38% (95% confidence interval [CI] 87.10% to 99.04%) and the positive agreement was 74.32% (95% CI 62.84% to 83.78%) between the 2 groups. Using the 2.8 ng/mL growth hormone cut-off point for macimorelin,

sensitivity was 87% and specificity 96%. Increasing the growth hormone cut-off point to 5.1 ng/mL for macimorelin increased the sensitivity to 92% but the specificity remained at 96%. No serious adverse events were reported for macimorelin. Non-serious adverse events were more common and of greater severity for the insulin tolerance test compared with the macimorelin test.

### Strengths and limitations

This phase 3 study concluded that macimorelin is a simple, well-tolerated, reproducible and safe test for diagnosing AGHD with accuracy comparable with the insulin tolerance test. The trial has several strengths; it included matched controls and evaluated people with a low, intermediate and high likelihood of having growth hormone deficiency (GHD). A study limitation was that a specific population was evaluated, which may limit the generalisability of the results. The trial was funded by the company and all authors received research support from the company. The authors have also presented the results in the form of a conference abstract (Garcia et al. 2017).

## Garcia et al. (2021)

### Study size, design and location

A post-hoc analysis from a phase 3 clinical trial in 41 people with a high likelihood of AGHD and 25 healthy matched controls in the US and 25 sites across Europe.

### Intervention and comparator

Macimorelin compared with the insulin tolerance test.

### Key outcomes

This was a post-hoc analysis of the Garcia 2018 trial. The performance of the macimorelin test, reported as area under the receiver operating characteristic curve, was not meaningfully affected by age (0.9924), body mass index (BMI; 0.9916) or sex (0.9950) compared with the unadjusted model (0.9924). Using the growth hormone cut-off point of 2.8 ng/mL for macimorelin, estimated sensitivity was 88% and specificity was 97% for the unadjusted model. These values remained the same when adjusting for age and for mean or median BMI. When adjusting for sex, sensitivity was 88% for both males and females, and specificity was 100% for males and 93% for females. Using the growth hormone cut-

off point of 5.1 ng/mL for macimorelin, estimated sensitivity was 93% and specificity was 97% for the unadjusted model. These values remained the same when adjusting for age and BMI but changed slightly when adjusting for sex. When evaluating the entire study population, using the same cut-off point of 2.8 ng/mL for both the macimorelin test and the insulin tolerance test resulted in high levels of positive (87.1%), negative (93.6%) and overall (90.7%) agreement between tests. These were higher than agreement levels using a cut-off point of 5.1 ng/mL for both tests. Of the 4 growth hormone cut-off points evaluated, the cut-off point of 5.1 ng/mL provided maximal specificity (96%) and high sensitivity (92%) and was in good overall agreement with the insulin tolerance test at the same cut-off point (87%).

### Strengths and limitations

The authors concluded that the macimorelin test performance is robust and not meaningfully affected by age, baseline BMI or sex over a range of growth hormone cut-off points. Limitations include a small sample size and limited generalisability to people aged 65 and over, people with poorly controlled diabetes or people with severe obesity. The study was sponsored by the company.

## Garcia et al. (2013)

### Study size, design and location

Multicentre open-label study in 50 people with AGHD and 48 healthy matched controls in the US.

### Intervention and comparator

Macimorelin compared with arginine plus growth hormone-releasing hormone (GHRH).

### Key outcomes

Peak growth hormone levels in the AGHD group were 2.36 ng/mL (standard deviation [SD] 5.69 ng/mL) compared with 17.71 ng/mL (SD 19.11 ng/mL) in the control group ($p<0.0001$). For macimorelin, the receiver operating characteristic analysis yielded an optimal growth hormone cut-off of 2.7 ng/mL, with 82% sensitivity and 92% specificity. There was a misclassification rate of 13%. In both groups, 58% of people had obesity and peak growth hormone levels were inversely associated with BMI in the control group. Using a separate

cut-off point of 6.8 ng/mL for people without obesity and 2.7 ng/mL for people with obesity increased the sensitivity to 86% and reduced the misclassification rate to 11%. In people receiving both tests, macimorelin showed a better discrimination compared with arginine plus GHRH, but this difference was not statistically significant (p=0.29). One serious adverse event, an asymptomatic QT interval prolongation on the electrocardiogram, was reported in a matched control group receiving macimorelin.

### Strengths and limitations

The authors concluded that this study showed that macimorelin is safe and effective in diagnosing AGHD, with sensitivity and specificity comparable with other tests. The study was originally designed as a crossover trial of macimorelin compared with arginine plus GHRH. However, after 43 people with AGHD and 10 controls had been tested, the GHRH used in the study became unavailable in the US. The study was completed by testing 10 more people with AGHD and 38 controls with macimorelin alone. People with diabetes, renal or hepatic dysfunction were excluded from the trial, potentially limiting the generalisability of the results. All investigators received research support from Ardana Biosciences, Aeterna Zentaris, or both.

## Sustainability

The company did not make any claims around environmental sustainability benefits for macimorelin.

## Recent and ongoing studies

The company states that there is an ongoing phase 3 study in paediatrics:

A Research Study of How Well Macimorelin Works to Find Out if Children Have a Lack of Growth Hormone and How Safe it is (DETECT). ClinicalTrials.gov identifier: NCT04786873. Status: recruiting. Indication: growth hormone deficiency. Drug: macimorelin. Estimated completion date: September 2023. Countries: Georgia, Italy, Poland, US.

# Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not

represent NICE's view.

All experts were familiar with macimorelin but had not used this technology before. Experts noted that macimorelin is not yet used in clinical practice in the NHS to diagnose adult growth hormone deficiency (AGHD), possibly because it has been licensed recently.

# Level of innovation

The experts agreed that macimorelin is the first and only oral test approved to diagnose AGHD. Experts noted that other tests are available to diagnose AGHD, such as arginine and glucagon stimulation tests, but that these are not administered orally or work through the growth hormone secretagogue receptor.

# Potential patient impact

The experts agreed that the potential patient benefits include that it is a less invasive test because of its oral administration, fewer blood samples and shorter procedure time, and that it is associated with fewer side effects. One expert noted that it may reduce travel time because it can be done at secondary district general hospitals instead of tertiary centres.

Experts identified multiple groups of people who could benefit from macimorelin, including those with a contraindication for the insulin tolerance test (for example, people with ischaemic heart disease, people aged 65 or older, and people with epilepsy) and people with uncontrolled diabetes or obesity who are at risk of test failure or inaccuracy with the insulin tolerance test and glucagon stimulation test. One expert also noted that it can be used for people who do not need their adrenocorticotropic hormone levels tested.

One expert noted that in their centre, macimorelin would be suitable for about 20 to 25 people per year. Another expert noted that their centre does about 100 insulin tolerance tests per year, but this also includes paediatrics and people who need testing for combined growth hormone and adrenocorticotropic hormone levels. The expert estimated that macimorelin would be suitable for about 1,000 to 1,500 adults per year in the UK.

# Potential system impact

Experts noted multiple system benefits associated with the use of macimorelin, including

that the test is less invasive; it has a shorter testing period and requires fewer blood samples to be taken and analysed, thus potentially requiring fewer staff and lab resources. Furthermore, it can be done in an outpatient setting instead of as a day case procedure. It requires fewer staff to monitor the person having the test because it does not induce hypoglycaemia, so cardiac monitoring and blood glucose monitoring are not needed. One expert noted that it has the potential to reduce waiting times because the insulin tolerance test is only offered in certain centres, leading to a delay in diagnosis and treatment for many people. All experts agreed that when considering all the costs and resources associated with doing the tests, macimorelin has the potential to be cost saving compared with standard care.

Two experts noted that tests with macimorelin can be done in most or all general hospitals. However, another expert clarified that this should be all specialist hospitals and endocrine tertiary clinics that can start and monitor growth hormone replacement therapy in adults. Experts noted that no change to existing facilities are needed. Two experts noted that it can be done in an outpatient setting, so the room needs to be suited for patient privacy and phlebotomy procedures.

Two experts agreed that training is needed because it is a new test. One expert clarified that this should be for the medical and nursing teams, mainly endocrine specialist nurses or other clinicians who have expertise in diagnosing and treating AGHD. The expert clarified that training would be so clinicians can identify the correct people for the test and inform them on what to expect from the test, and that it is not meant for mass testing. The other expert noted that the training would not be extensive because it involves a simple protocol for use.

# General comments

All experts noted that macimorelin has the potential to replace some of the insulin tolerance tests or glucagon stimulation tests, specifically when these other tests are contraindicated or unable to be used because of limited resources or expertise. Two experts said that macimorelin can only test for growth hormone deficiency, but the insulin tolerance test and glucagon stimulation test are dynamic and can also diagnose adrenocorticotropic hormone deficiency by measuring the cortisol axis. This may be relevant for people after anterior pituitary surgery or radiotherapy. One expert noted that they are now moving towards using the short synacthen test, provided adrenal gland atrophy has occurred after surgery, to get information on the cortisol axes and that this cannot diagnose growth hormone deficiency. In these cases, the growth hormone axis is

usually tested at a later stage, for which macimorelin could become the preferred standard of care.

The experts said that overall, there are no issues that would prevent macimorelin from being used in the NHS. However, the experts noted that the emphasis can be on the cost of macimorelin alone, rather than taking all the associated resources into account, which then may hinder adoption.

All experts noted that further research is needed, including research on its tolerability, the effect of body mass index on its effectiveness and in people for whom the insulin tolerance test is contraindicated. One expert also noted that research on the reliability of macimorelin in people with radiation-induced hypopituitarism would be valuable. One expert noted that macimorelin has not been evaluated in children yet.

# Patient organisation comments

Key benefits for patients identified by patient organisations include that the test itself is less invasive, quicker to perform and has reduced side effects compared with other tests. No disadvantages about possible side effects or practical difficulties were raised, apart from if there are known side effects for particular patient groups. Both patient organisations noted that macimorelin can be used for anyone who has a suspected growth hormone deficiency. One patient organisation specified that this could include people with diagnosed pituitary issues or people with severe head injury. They also noted that people with mental health issues or anxiety may particularly benefit from macimorelin because some people have refused the insulin tolerance test because of the side effects and the stress it caused them. The patient organisations did not identify any subgroups that need special consideration for using macimorelin. Both patient organisations highlighted that macimorelin is vital for patient safety and comfort and should be available for anyone who needs testing for adult growth hormone deficiency.

# Expert commentators

The following clinicians contributed to this briefing:

- Robert Murray, consultant endocrinologist and honorary associate professor, Leeds Teaching Hospitals NHS Trust. Received a fee for chairing a symposium organised by Consilient Health in April 2022.

- Dr Sofia Llahana, National Institute for Health Research (NIHR) and Health Education England (HEE) post-doctoral clinical lecturer, University of London and University College London Hospitals NHS Foundation Trust. Did not declare any interests.
- Sherwin Criseno, nurse consultant in endocrinology, University Hospitals Birmingham NHS Foundation Trust. NIHR and HEE clinical doctoral research fellow and co-chair of the UK macimorelin advisory board in 2022.

Representatives from the following patient organisations contributed to this briefing:

- The Pituitary Foundation.
- Child Growth Foundation.

# Development of this briefing

This briefing was developed by NICE. The interim process and methods statement for medtech innovation briefings sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-5108-6