Reference number: 2402
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Clinical Commissioning Policy:

Lonafarnib for Hutchinson-Gilford progeria syndrome (12 months of age and over) [URN:2402]

Summary

Lonafarnib is recommended to be available as a routine commissioning treatment option for Hutchinson-Gilford progeria syndrome (HGPS) within the criteria set out in this document. Lonafarnib is indicated for the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome or a processing-deficient progeroid laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation.

The policy is restricted to patients aged 12 months and over with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome with a heterozygous LMNA mutation with progerin-like protein accumulation in line with the findings of the evidence review.

Committee discussion

Clinical Panel agreed with the policy and recommended this proceeds as a routine commissioning policy. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group (CPAG) are asked to consider the evidence and the policy. The CPAG committee papers can be accessed here: Clinical commissioning policy: Lonafarnib for Hutchinson-Gilford progeria syndrome (12 months of age and over)

What we have decided

NHS England has carefully reviewed the evidence to treat patients with HGPS with lonafarnib. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed here: Clinical commissioning policy: Lonafarnib for Hutchinson-Gilford progeria syndrome (12 months of age and over)

Links and updates to other policies

NHS England has no other policies relating to the use of lonafarnib.

Plain language summary

About Hutchinson-Gilford progeria syndrome (HPGS)

Progeroid laminopathies are rare, fatal genetic conditions characterised by an appearance of accelerated aging in children. The majority of patients with progeroid laminopathies have the type, HGPS. This condition is also known as ‘progeria’.

A specific pathogenic variant (gene change) in the LMNA gene, located on chromosome 1, is responsible for HGPS. This genetic variant is sporadic and occurs without family history. The LMNA gene produces the Lamin protein, which is part of the structural scaffolding that holds the nucleus of a cell together. It is believed that the defective Lamin A protein makes the nucleus unstable. That cellular instability leads to the process of premature aging.

Although individuals are born appearing healthy, children with progeria begin to display many characteristics of accelerated aging within the first two years of life. Progeria signs include growth failure, loss of body fat and hair, aged-looking skin, stiffness of joints, hip dislocations, atherosclerosis, cardiovascular disease and stroke. Children with progeria have significant physical disability and require help with all activities of daily living, but they are cognitively normal. Children with progeria usually die of atherosclerosis (heart disease) at an average age of 14.5 years.

About current treatment

Current standard of care involves multi-disciplinary clinical monitoring by local teams with monitoring of growth and weight, bone density scans, dental reviews, cardiology reviews, hearing tests and psychological support due to visible differences.

Treatment is supportive and does not involve attempting to reduce the accumulation of progerin and its expression. Examples of supportive care include hearing aids; ocular lubrication for exposure keratopathy; tooth extractions for dental crowding; physical and occupational therapy for skeletal abnormalities and joint contractures and annual cardiac screening. Mortality in these patients is usually attributed to cardiovascular complications, therefore supportive treatments aim to reduce cardiovascular sequelae, such as low-dose aspirin, statins to lower cholesterol, antihypertensives and anticoagulants. These medications may not be started at the time of diagnosis but are started when felt to be clinically needed.

About lonafarnib treatment

Lonafarnib is a potent and specific inhibitor of farnesyltransferase, therefore blocking the farnesylation of progerin and reducing the accumulation of progerin and progerin-like proteins in the cells.

Lonafarnib is licensed for the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of HGPS or a processing-deficient progeroid laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation. The licence is outlined in the Medicines and Healthcare products Regulatory Agency (MHRA) approved Summary of Product Characteristics (SmPC) for either 50mg or 75mg capsules.

This policy is restricted to patients 12 months of age and older with a genetically confirmed diagnosis of HGPS with a heterozygous LMNA mutation with progerin-like protein accumulation in line with the findings of the evidence review.

Epidemiology and needs assessment

HGPS occurs in approximately 1 in 4 - 8 million newborns (incidence), affecting both sexes and all races equally (Hennekam, 2006). The prevalence of HGPS is estimated to be approximately 1 in 23 million (Wang et al, 2024). It is estimated that approximately 3-4 patients would receive lonafarnib every year in England.

Implementation

NHS England will routinely commission lonafarnib in accordance with the patient pathway for patients meeting **all** of the following inclusion criteria, and **none** of the exclusion criteria.

Inclusion criteria

Patients aged 12 months of age and older with a genetically confirmed diagnosis of:

- HGPS

  AND

- Associated with a heterozygous LMNA mutation with progerin-like protein accumulation.

Exclusion criteria

Patients who meet **ANY** of the following criteria are not eligible for treatment with lonafarnib under this policy:

- In patients with severe hepatic impairment (Child-Pugh Class C) where lonafarnib is contraindicated;
- Hypersensitivity to the active substance or any other member of the farnesyltransferase class, or to any of the excipients listed in section 6.1 of the Medicines and Healthcare products Regulatory Agency (MHRA) approved Summary of Product Characteristics (SmPC) for either 50mg or 75mg capsules;
- Concomitant use with strong CYP3A inhibitors;
- Concomitant use of medicinal products that are predominantly metabolised by CYP3A4, such as midazolam, atorvastatin, lovastatin and simvastatin;
- In patients considered unsuitable for treatment with lonafarnib after Prescribing Planning meeting discussion.

Starting criteria

Patients who fulfil the criteria for treatment of lonafarnib should be discussed in a Prescribing Planning meeting before starting treatment. It is recommended that the meeting should include the clinical geneticists involved in confirming the diagnosis, the referring clinician (if appropriate), and specialists involved in the ongoing care of the patient. It should be agreed who the named clinician or team responsible for prescribing and overseeing the monitoring of lonafarnib treatment will be, and the frequency with which this meeting will take place to review the patient and lonafarnib treatment.

Before starting lonafarnib, all patients should have an electrocardiogram (ECG) done to rule out QTc prolongation. Blood tests to check the levels of potassium, calcium, and magnesium should also be performed before starting treatment. Lonafarnib can interact with a number of medications, so medications should be reviewed, and further information can be found in the relevant MHRA approved SmPC: 50mg or 75mg capsule.

Stopping criteria

Treatment will be stopped in patients who meet **ANY** of the following criteria:

- Serious adverse events including anaphylaxis

  OR

- Unacceptable toxicity as specified by the MHRA approved SmPC.

Dosing

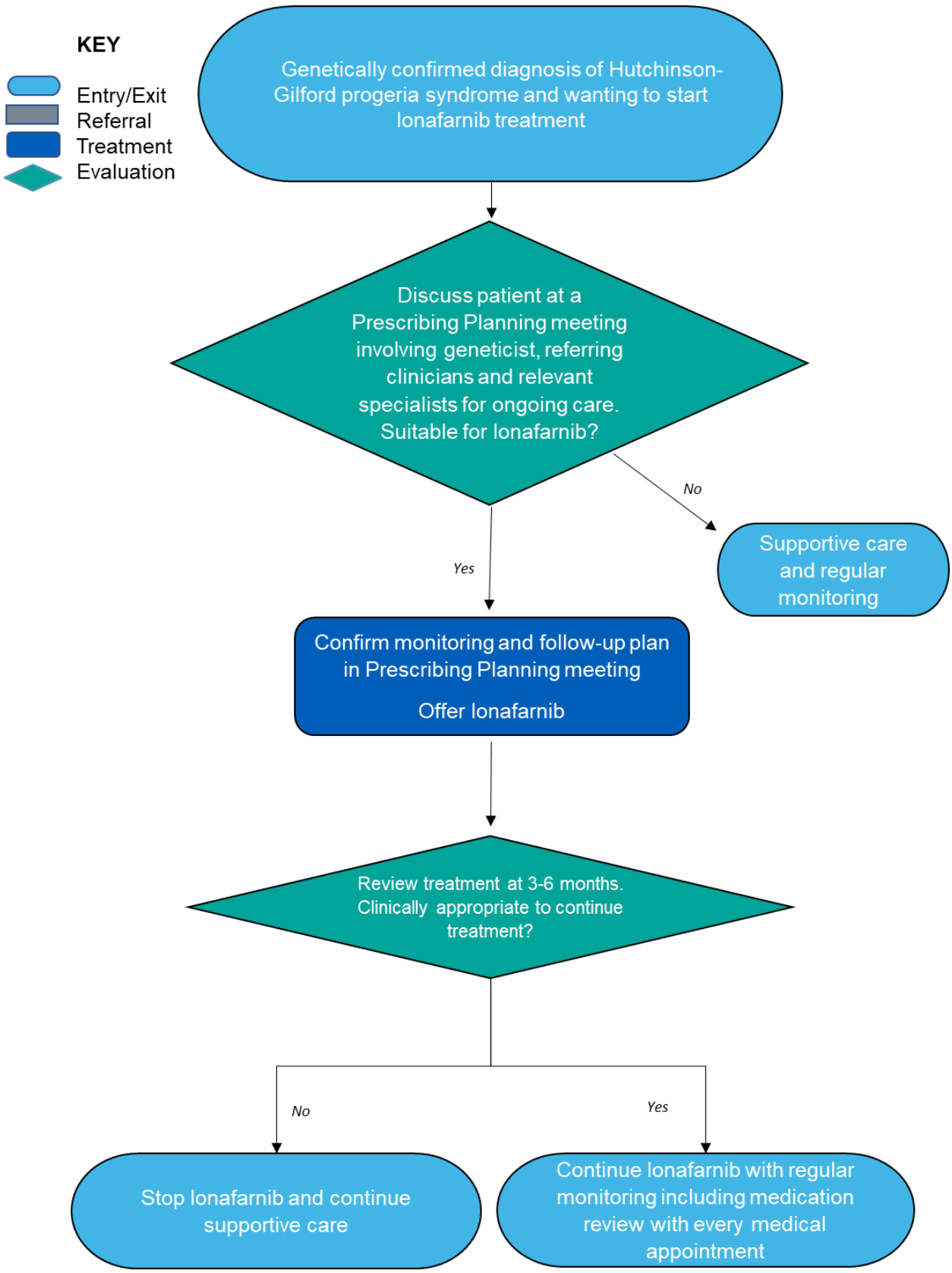
Lonafarnib is available in 50mg and 75mg capsules and recommended dosing is twice daily with food. It is dosed according to body surface area (BSA). Dosing should be in accordance with the relevant MHRA approved SmPC: 50mg or 75mg capsule.

If capsules cannot be swallowed whole, capsules can be opened and the contents of the capsule can be mixed with orange juice, guidance is provided in Section 6.6 of the relevant MHRA approved SmPC.

Monitoring

The clinician or team responsible for overseeing the monitoring of lonafarnib must be agreed at the Prescribing Planning meeting. A summary of any meetings must be recorded in the patient notes. Patients on lonafarnib should be regularly monitored at their appointments with each specialist team, to ensure they are suitable to continue and tolerating treatment. This should include at least annual review of blood tests including renal function and liver function tests, as well as an ECG and review of all medications. Height and weight should be monitored every 6 months.

Patient pathway



Governance arrangements

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

Lonafarnib within the criteria set out in this document will be commissioned and funded by NHS England under existing arrangements for the provision of specialised services.

Audit requirements

Provider organisations must ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

The prescribing clinician/organisation is responsible for registering the patient using the following form which will be provided by the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). Additional outcomes defined by NHS England must be collected locally as baseline data, monitored at the Prescribing Planning meeting and reported on an annual basis using the form.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment, and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Chromosome	A chromosome is a thread-like structure composed of DNA and proteins found in the nucleus of most living cells. Chromosomes carry genetic information in the form of genes.
Farnesylated	Farnesylated refers to a protein that has undergone a specific type of post-translational modification. This process involves the addition of a farnesyl group (a type of lipid) to a cysteine residue near the protein's end. This modification helps the protein attach to cell membranes, which is crucial for its function, especially in cellular signaling.
Genetic disorder	A genetic disorder is a health condition caused by abnormalities in an individual's DNA. These abnormalities can be due to mutations in a single gene, multiple genes, or changes in the structure or number of chromosomes.
Heterozygous	Heterozygous refers to having two different alleles of a particular gene. It means that an individual has inherited different versions of a gene from each parent.
Homozygous	Homozygous refers to having two identical alleles of a particular gene. In simpler terms, it means that an individual has inherited the same version of a gene from both parents.
Keratopathy	Keratopathy refers to a group of diseases affecting the cornea, the clear, dome-shaped surface that covers the front of the eye. These conditions can lead to various symptoms, including inflammation, irritation, redness, pain, clouding, or scarring of the cornea, and reduced vision.
Nucleus	The nucleus is the control centre of a cell. It holds the cell's genetic material (DNA) and manages activities such as growth, metabolism, and reproduction.
Pathogenic	The term pathogenic refers to the ability to cause disease. Specifically, it describes organisms, such as bacteria, viruses, fungi, or parasites, that can produce illness in their host.
Protein	A protein is a large, complex molecule that plays many critical roles in the body. Proteins are made up of long chains of amino acids, which are linked together by peptide bonds. They perform a vast array of functions within organisms, including catalyzing metabolic reactions, replicating DNA, responding to stimuli, and transporting molecules.

References

Hennekam, R.C., 2006. Hutchinson–Gilford progeria syndrome: review of the phenotype. American journal of medical genetics Part A, 140(23), pp.2603-2624.

Wang, J., Yu, Q., Tang, X., Gordon, L.B., Chen, J., Jiang, B., Huang, G., Fu, H., Qian, J., Liu, Z. and Mao, J., 2024. Epidemiological characteristics of patients with Hutchinson-Gilford progeria syndrome and progeroid laminopathies in China. Pediatric Research, 95(5), pp.1356-1362.