

**NIHR Innovation Observatory
Evidence Briefing: July 2017****Arimoclomol for Niemann-Pick Disease type C -
add-on therapy**

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LAY SUMMARY

Niemann-Pick Disease is a group of rare, inherited disorders that is divided into three main types (A, B and C), based on the gene mutations and symptoms involved. Niemann-Pick disease type C (NPC) is caused by a particular gene mutation which results in the accumulation of fatty substances (lipids) in the cells of the liver, brain and spleen. Therefore, many normal cell functions are impaired. This leads to cell death, causing the tissue and organ damage seen in NPC. NPC is a devastating and life-threatening condition that presents considerable challenges for patients and their families.

Arimoclomol is a medicine that is under investigation as a treatment for NPC. It is given by mouth as capsules. Arimoclomol helps the body's cells to process accumulated lipids. If licensed, arimoclomol could offer an additional treatment option for people with NPC.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Niemann-Pick disease (Niemann-Pick disease type C (NPC))

TECHNOLOGY

DESCRIPTION

Arimoclomol (Arimoclomol [INN]; BRX-220; OR-01; OR-04) is under development for the treatment of Lysosomal Storage Diseases such as NPC and Gaucher's disease. The drug is administered orally. It acts by targeting heat shock protein 70 (Hsp70).^{1, 2}

Arimoclomol works by causing the up-regulation of molecular chaperones in cells that includes Hsp70, which functions as a chaperone. Molecular chaperone proteins are critical in the cellular response to stress and protein misfolding. Arimoclomol is a small molecule activator of chaperones in cells under stress. Its function is to amplify molecular chaperone proteins, normally found in all cells of the body and thought to enhance the cell's natural ability to mend damaged, misfolded proteins.¹ In lysosomal storage diseases such as NPC, Hsp70 helps to fold the digestive enzyme into a functional conformation, allowing the cell to process the accumulated lipid.² Also, arimoclomol protects neurons from protein aggregation and toxicity (Parkinson disease, Alzheimer disease, polyglutamine diseases, and amyotrophic lateral sclerosis), protects cells from apoptosis (Parkinson disease).¹

In the phase II/III clinical trial (NCT02612129), subjects in the experimental arm receive arimoclomol capsules for oral administration (3 times daily); doses: 150-600 mg/day (based on weight) for 12 months. Following this, all patients will be offered to continue into the extension phase of the study.³

Arimoclomol does not currently have Marketing Authorisation in the EU for any indication. However, in the EU, arimoclomol has been awarded an Orphan Drug Designation for NPC,⁴ Amyotrophic Lateral Sclerosis,⁵ and Inclusion Body Myositis.⁶ Furthermore, in the USA, arimoclomol has been awarded an Orphan Drug Designation for NPC and Amyotrophic Lateral Sclerosis.^{1, 7}

This product is in phase II/III development for Amyotrophic Lateral Sclerosis, Sporadic Inclusion Body Myositis (s-IBM).⁸

INNOVATION and/or ADVANTAGES

There is currently significant unmet need for the treatment of NPC. The European Medicines Agency indicated that arimoclomol might be of significant benefit for patients with NPC because it works in a different way to the current available drug (miglustat) and studies suggest it might be of benefit in reducing the symptoms of the disease.⁴

DEVELOPER

Orphazyme ApS

AVAILABILITY, LAUNCH or MARKETING

Arimoclomol is a designated orphan drug in the EU/USA for Niemann-Pick Disease Type C.^{4, 7}

PATIENT GROUP

BACKGROUND

Niemann-Pick disease (NPD) is a group of diseases passed down through families (inherited). NPD has a wide range of symptoms that vary in severity. NPD is divided into three main types: type A, type B, type C (includes type C1 and type C2). These types are classified on the basis of genetic cause and the signs and symptoms of the condition.^{9,10}

NPD is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Niemann-Pick disease type C (NPC) is caused by mutations in either the Niemann-Pick type C1 (NPC1) gene or type C2 (NPC2) gene.⁹ Approximately 95 % of NPC cases are caused by genetic mutations in the NPC1 gene, with the other 5% caused by mutations in the NPC2 gene.¹¹ The proteins produced from these genes are involved in the movement of lipids within cells. Mutations in these genes lead to a shortage of functional protein, which prevents movement of cholesterol and other lipids, leading to their accumulation in cells. Because these lipids are not in their proper location in cells, many normal cell functions that require lipids (such as cell membrane formation) are impaired. The accumulation of lipids as well as the cell dysfunction eventually leads to cell death, causing the tissue and organ damage seen in NPC1 and NPC2.⁹

The signs and symptoms of NPC1 and NPC2 are very similar; these types differ only in their genetic cause. NPC1 and NPC2 usually become apparent in childhood, although signs and symptoms can develop at any time. People with these types usually develop difficulty coordinating movements (ataxia), an inability to move the eyes vertically (vertical supranuclear gaze palsy), poor muscle tone (dystonia), severe liver disease, and interstitial lung disease. Individuals with NPC1 and NPC2 have problems with speech and swallowing that worsen over time, eventually interfering with feeding. Affected individuals often experience progressive decline in intellectual function and about one-third have seizures. People with these types may survive into adulthood.⁹

CLINICAL NEED and BURDEN OF DISEASE

The incidence of NPC is widely reported at 1 in 120,000, although recent evidence suggests this may be an under-estimate.¹¹ NPC affected approximately 0.1 in 10,000 people in the EU in 2014.⁴ The true prevalence of NPC is difficult to assess due to insufficient clinical awareness combined with the relative difficulty of biochemical testing. Estimates of prevalence at birth ranging between 0.66 and 0.83 per 100,000 were proposed for France, the UK and Germany based on diagnoses made in a laboratory setting over the period 1988-2002.¹²

NPC is now recognised as a relatively common cause of liver disease in early life. Fetal hydrops or fetal ascites can be observed. Above all, a prolonged neonatal cholestatic icterus, appearing in the first days or weeks of life and usually associated with progressive hepatosplenomegaly is present in close to half of patients, although with very variable intensity. In most cases, the icterus resolves spontaneously by 2 to 4 months of age, and only hepatosplenomegaly remains for a highly variable period, preceding onset of neurologic symptoms. In about 10% of these patients, however, the icterus quickly worsens and leads to liver failure. Children with this dramatic "acute" neonatal cholestatic rapidly fatal form usually die before the age of 6 months. Some other infants, especially (but not exclusively) those having mutations in the NPC2 gene, present with a severe respiratory insufficiency (together with hepatosplenomegaly or more severe liver disease) that may also be fatal.¹² Apart from a small subset of patients who die at birth, or in the first 6 months of life from hepatic or respiratory failure, and exceptional adult cases, all patients ultimately will develop a progressive and fatal neurological

disease. Systemic disease, when present, always precedes onset of neurological symptoms, but the systemic component may be absent or minimal in approximately 15% of all patients, and close to half of the adult-onset patients, at least at the time of diagnosis. In typical patients, the neurologic disorder consists mainly of cerebellar ataxia, dysarthria, dysphagia, and progressive dementia, and the majority of cases show a characteristic vertical supranuclear gaze palsy (VSGP). Cataplexy, seizures, and dystonia are other quite common features, and psychiatric disturbances are frequent in late-onset patients.¹²

The population likely to be eligible to receive arimoclomol could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2016/17 Manual for Prescribed Specialised Services. Publications Gateway Reference 05233.
- NHS England. 2013/14 NHS Standard Contract for Lysosomal Storage Disorders Service (Children). E06/S (HSS)/c.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). E06/S/a.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Laboratory Services). E06/S/c

OTHER GUIDANCE

- NP-C Guidelines Working Group. Recommendations for the diagnosis and management of Niemann–Pick disease type C: An update. 2012.¹³
- Niemann-Pick Guideline Development Group. Management of Niemann-Pick Type A & B Diseases (Acid Sphingomyelinase Deficiency): A Clinical Guideline. version 22 Oct 2015.¹⁴
- Niemann-Pick type C (NPC): Canadian Management Guidelines.¹⁵

CURRENT TREATMENT OPTIONS

There is no cure for NPC, although patients benefit from palliative treatments (individual medications that will help to treat the symptoms related to the condition). In the absence of any curative treatment, quality of life represents a legitimate treatment goal in the management of NPC, and can be addressed by:

- 1) Rigorous symptomatic treatment;
- 2) Miglustat therapy (Zavesca®) for existing neurological manifestations.

Occupational therapy can be used to help with posture, speech and movement. In 2009, the European Medicines Agency approved the use of Zavesca for the treatment of progressive neurological manifestations in adult and paediatric patients with NPC. Zavesca has been shown to delay the progression and stabilise certain symptoms of the disease. However, this drug is not suitable for every affected individual therefore it is advised that the individual to discuss all medical issues the doctor.^{11,13}

EFFICACY and SAFETY

Trial	NCT02612129; Patients Diagnosed With NiemannPick Disease Type C aged 2 to 18 Years; Arimoclolmol vs Placebo; both as an add-on therapy to the patient's current prescribed best standard of care; phase II/III
Sponsor	Orphazyme ApS
Status	Ongoing
Source of Information	Trial registry. ³
Location	Eight EU countries (incl UK) and USA.
Design	Randomised, placebo-controlled, double-blind.
Participants	n= 46 (planned); aged 2-18 years; males and females; NPC; genetically confirmed by mutations in both alleles of NPC1 or NPC2, or mutation in only one allele of NPC1 or NPC2 plus either positive filipin staining or elevated cholestane triol/oxysterols (>2 x upper limit of normal).
Schedule	Randomised to arimoclolmol capsules for oral administration (3 times daily), doses: 150-600 mg/day (based on weight); or placebo capsules; both in combination with their ongoing standard of care for 12 months.
Follow-up	The duration of the blinded phase study period will be 12 months. Following this, all patients will be offered to continue into the extension phase of the study where every patient will receive arimoclolmol, follow-up at 18 months, 24 months (after randomisation) and then on an annual basis thereafter. The extension phase runs until arimoclolmol has received Regulatory Approval or until the analysis of data from the controlled, blinded phase 12 month study period does not support the efficacy and/or safety of arimoclolmol.
Primary Outcomes	<ul style="list-style-type: none"> • Change in NPC disease severity score - baseline (Visit 1) to 12 months • Change in the NPC disease severity based on the NPCCSS scores
Secondary Outcomes	<ul style="list-style-type: none"> • Change in the Niemann Pick type C Clinical Database (NPC-cdb) score - baseline (Visit 1) to 6 months, 12, 18, 24 and 36 months. • Change in NPCCSS score - baseline (Visit 1) to 6 months, 18, 24 and 36 months • Change in NPCCSS score (individual domains) - baseline (Visit 1) to 6 months, 12, 18, 24 and 36 months • Change in Quality of Life (EQ5DY) - baseline (Visit 1) to 6 and 12 , 18, 24 and 36 months • Change in the SARA score - baseline (Visit 1) to 6 and 12 , 18, 24 and 36 months • Change in the 9HPT (9 Hole Peg Test) - baseline (Visit 1) to 6 and 12 , 18, 24 and 36 months • Adverse events (AEs) - Baseline (visit 1) - 36 months
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study [or Primary] completion date reported as December 2017.

ESTIMATED COST and IMPACT

COST

The cost of arimoclomol is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|---|--|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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