Diazoxide choline controlled-release for Prader-Willi syndrome – first line

NIHR HSRIC ID: 10699

Lay summary

Diazoxide choline is a new drug to treat Prader-Willi syndrome. Prader-Willi syndrome is a rare genetic disorder that causes people to eat uncontrollably and become obese. It may also cause learning difficulties and behavioural problems. Diazoxide choline is a slow release tablet that is taken by mouth. Some studies have suggested that diazoxide choline may help people with Prader-Willi syndrome to control their eating.

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

- Prader-Willi Syndrome (PWS): paediatric and adult patients – first line.

TECHNOLOGY

DESCRIPTION

Diazoxide choline controlled release (DCCR) is a tablet formulation of the choline salt of diazoxide. In the hypothalamus, deficiencies or resistance to insulin or leptin leads to dysregulation of appetite and energy expenditure, and ultimately to overeating and excess weight gain. Studies have suggested that the molecular end-point for the leptin activated pathway in the hypothalamus is the opening of the adenosine triphosphate potassium (KATP) channel. DCCR acts as a KATP channel agonist, thereby potentially overcoming the hypothalamic resistance to leptin and/or insulin. In patients with PWS, this KATP activation in the hypothalamus may reduce the central starvation signal, reduce synthesis of new fatty acids in adipocytes, increase beta-oxidation of fat, improve gamma-aminobutyric acid (GABA) response in GABAergic neurons and limit excess atrophy in skeletal muscle. DCCR is taken orally once a day.

DCCR does not currently have a Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, DCCR will offer the first treatment with the potential to control appetite and obesity in patients with PWS. DCCR may also reduce aggressive and destructive behaviour.

DEVELOPER

Essentialis, Inc.

AVAILABILITY, LAUNCH OR MARKETING

DCCR is a designated orphan drug in the USA.

PATIENT GROUP

BACKGROUND

PWS is a genetic disorder that causes childhood obesity. About 70% of PWS are caused by a deletion in region 15q11-q13 on chromosome 15 inherited from the father. About 25-30% of cases are due to an individual inheriting two chromosome 15s from the mother and none from the father, known as uniparental disomy. A small number are also due to translocation or imprinting irregularities of chromosome 15.

Symptoms of PWS begin in infancy with hypotonia. Weak cry and suck reflex are typical, which result in babies unable to breastfeed and requiring tube feeding. As children grow older, strength and muscle tone may improve, but typically patients require growth hormone.
injections to overcome hypotonia\textsuperscript{a}. Children with PWS develop an unregulated appetite between the ages of 3 to 8 years\textsuperscript{a}. Individuals lack normal hunger and satiety cues, resulting in overeating if not carefully monitored\textsuperscript{b}. Other features of PWS may include hypogonadism, obesity due to excessive appetite and overeating (hyperphagia), central nervous system and endocrine gland dysfunction that causes varying degrees of learning disability, short stature due to growth hormone deficiency, somnolence and poor emotional and social development\textsuperscript{3}. The behavioural characteristics may include temper outbursts, compulsivity, poor impulse control and oppositional behaviour\textsuperscript{4}. Men with PWS have an average final adult height of about 154cm, while women have a final adult height of 145–159cm\textsuperscript{5} in individuals who have not been treated with growth hormone\textsuperscript{a}.

**CLINICAL NEED and BURDEN OF DISEASE**

PWS occurs in about 0.4 to 0.67 per 10,000 live births\textsuperscript{5}. PWS affects males and females equally, and is found in all ethnic groups\textsuperscript{2}. Once hyperphagia sets in, without adequate weight control and healthy eating management, individuals with PWS will become obese and suffer from associated complications such as diabetes, obstructive sleep apnoea, and right-sided heart failure, with death typically occurring in the fourth decade of life\textsuperscript{6} (although according to the PWSUSA database, the average age of death was 29 years\textsuperscript{a}). Mortality among PWS patients is elevated at all ages and is between 2 and 3 fold that of the general population\textsuperscript{b}. However, with careful weight control and behavioural management, people with PWS may live healthy lives into older adulthood\textsuperscript{6}.

In 2014-15, there were 267 admissions for PWS (ICD-10 Q87.1) in England, resulting in 880 bed days and 282 finished consultant episodes\textsuperscript{7}.

According to the Prader-Willi Syndrome Association (PWSA)-UK registry, the estimated population prevalence in the UK is between 1,200 and 2,000 people\textsuperscript{a}.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**NHS England Policies and Guidance**


**Other Guidance**


\textsuperscript{a} Patient group personal communication.

\textsuperscript{b} Company information.

CURRENT TREATMENT OPTIONS

There is currently no cure for PWS with most research targeting specific symptoms. Adequate and appropriate nutritional intake must be maintained for all ages. Nasogastric tubes may be used when needed for infants who have poor feeding due to weak suck. Before hyperphagia becomes established, caloric restriction must be initiated, often to as little as 60% of the calories that similarly sized children without PWS might require for adequate growth. Careful attention is needed to provide a diet with balanced essential nutrients.

Human growth hormone is used for patients with PWS to treat short stature, muscle weakness, decrease body fat, improve weight distribution, and increase bone mineral density and stamina. There are no treatments to regulate appetite, which ultimately hinders the ability to live independently.

When hyperphagia develops, children with PWS may develop a range of food-related behaviours, including actively seeking food, eating non-food items, stealing to buy food or leaving home to search in wider area for food. These behaviours can be controlled by using strategies to limit access to food (e.g. locks on cabinets and refrigerators), limiting exposures that make the child think about food (e.g. avoiding birthday treats sitting on the teacher's desk during the school day), and instilling confidence that the next meal will be served on time by scrupulously maintaining mealtime routines. Parents should be counselled on dealing with these and other behavioural issues (such as obsessive compulsive disorder, and tobacco use or psychosis that may develop in adolescence).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02034071, PC025; DCCR vs placebo; phase I.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Essentials, Inc.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
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<tr>
<td>Location</td>
<td>USA.</td>
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<tr>
<td>Participants</td>
<td>n=13; aged 10-22 years; PWS; otherwise generally healthy; body mass index &gt;95th percentile; fasting glucose ≤126 mg/dL; HbA1c ≤6.5%.</td>
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<td>Schedule</td>
<td>Part 1: patients receive up to 4 dose levels of DCCR starting at 1.5mg/kg (maximum starting dose 145mg), and titrated every 14 days to 2.4mg/kg, 3.3mg/kg, and 4.2mg/kg (maximum dose of 507.5mg). Patients showing increase in resting energy expenditure and/or a reduction in hyperphagia through day 55 or 69 (responders) will then be randomised either to continue DCCR or placebo for an additional 4 weeks (Part 2). Non-responders will continue in open-label treatment during this extension period.</td>
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Follow-up

Part 1: active treatment up to day 69. Part 2: active treatment for 4 weeks (up to day 97). This was followed by a 6 mth open label treatment period.

Primary outcomes

Hyperphagia (assessed using hyperphagia questionnaire) and resting energy expenditure (Part 2).

Secondary outcomes

Weight; resting energy expenditure; hyperphagia (assessed using hyperphagia questionnaire); percent body fat; lean body mass; behavioural assessment; lipids. No quality of life measurement included in trial outcomes.

Key results

At the end of Part 1, there was significant improvement in hyperphagia (improvements seen in >90% of participants, overall reduction of -32%, p=0.003) which persisted throughout the treatment period and continued for those in Part 2 receiving DCCR but regressed in those switching to placebo. Improvement of hyperphagia was dose dependent.

For Part 1, improvements were noted in body fat mass (-3.8%, p=0.011, 75% responded with improvement), lean body mass (+5.4%, p=0.001, 90% responded with improvement), lean body mass/fat mass ratio (+9.8%, p=0.002, 100% responded with improvement), with reductions in waist circumference (-3.5cm, p=0.003) and in leptin (-22%, p=0.007). There was clinically relevant and statistically significant improvements seen in aggressive, threatening and destructive behaviour (-62.5%, p=0.01). The effects on body composition showed strong dose dependence.

In Part 1 and Part 2, treatment resulted in a 42% reduction in triglycerides, an 11% reduction in total cholesterol, a 25% increase in HDL cholesterol and a 13% reduction in non-HDL cholesterol. There was also improved insulin sensitivity as measured by HOMA-IR (−44%, p=0.095).

Adverse effects (AEs)

DCCR was well tolerated with most adverse events being of mild to moderate severity and improving or resolving as dosing continued.

ESTIMATED COST and IMPACT

COST

The cost of DCCR is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: improved family dynamics, reduced stress. The diazoxide formulation may represent a potential breakthrough in appetite and weight control and thus in behaviour in PWS. Expert from patient group states ‘DCCR is potentially good for PWS in that it seems to improve body composition (increasing stamina is important to families), may decrease hyperphagia and decrease destructive behaviour – ‘I think this is extremely important and sometimes overlooked as so critical for the family.

- No impact identified

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c Homeostasis Model Assessment (HOMA) estimates steady state beta cell function and insulin sensitivity, as percentages of a normal reference population
d Patient group personal communication.
Temper outbursts can be a huge problem - in very bad cases it can mean kids have to be taken out of their homes (if they are a threat to siblings) also limits school, work, and social engagement. A very big social impact.

An expert also noted that diazoxide is currently licensed for regulating insulin levels in insulin secreting tumours and disorders of low insulin and it has a long safety record, though the USA FDA issued a warning in 2015 of very rare instances of pulmonary hypertension in infants who had diazoxide for uncontrolled low blood sugar. This resolved when the diazoxide was discontinued. No events were reported for the DCCR trial for PWS and the dosing was 5 times lower than that which caused these rare isolated adverse events. The drug has also been shown to protect the heart from injury; the hypothesis being that KATP opening may facilitate insulin and leptin regulation, both key hormones in appetite and glucose metabolism, respectively.

Impact on Health and Social Care Services
- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- None identified
- Other:
  - a patient group commented that reduced social care funding has the potential to impact adversely on PWS community care resources. Anecdotal evidence from parents and carers indicates that educational, social and psychological support resources are in increasingly restricted or reduced supply for PWS families.

One parent from a patient organisation stated 'In the UK, parent consensus is that gaps are inconsistent dependant on borough/ funding. In my experience there is little knowledge [among] general clinicians, e.g. GP’s and A&E staff, when dealing with the unique complexities of PWS.

Impact on Costs and Other Resource Use
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs: may decrease costs related to obesity.
- None identified
- Other:
- Other:

* Patient group personal communication.
Clinical uncertainty or other research question identified: a patient group expert commented – the initial phase I trial (NCT02034071) was small and started as an observational study; and an unspecified proportion (likely 90%) went onto the second part of the trial as a randomised cohort, which showed improvements in hyperphagia, weight control, lipid metabolism and body fat composition. The manufacturer reported data references improved leptin profile (thus suggestive of decreased leptin resistance in leptin-replete individuals) and insulin sensitivity (as expected) and improved behaviour (aggression, destructive or threatening behaviour) -- and though welcome and promising -- must be interpreted with caution as these were not pre-specified outcome measures. Direct communication with manufacturer has confirmed mild peripheral oedema that resolved on discontinuation and posed no significant clinical problem. There were no reports of thrombosis in any participants in this PWS or other studies in the literature, which is clinically relevant and reassuring, as pulmonary embolism may account for up to 6% of deaths in PWS.

REFERENCES