DRAVET SYNDROME PIPELINE 2018

Dravet syndrome pipeline and opportunities review | July 2018

Dravet syndrome is a genetic neurological rare disease characterized by refractory epilepsy, intellectual disability, behavioral and movement disorders and a high mortality rate. The treatment approaches for this syndrome are currently limited to the symptomatic management of epileptic seizures. In recent years Dravet syndrome has received significant attention from the pharmaceutical industry, and the pipeline has matured to include not only symptomatic but also disease-modifying treatments. In June 2018, Epidiolex (cannabidiol oral formulation) from GW Pharmaceuticals obtained marketing authorization by the FDA, becoming the first drug to be approved for the treatment of Dravet syndrome in the US market. As of July 2018, Epidiolex is followed by ZX008 from Zogenix, close to filing for marketing authorization, and at least 7 additional symptomatic treatments that include second-generation cannabidiol formulations and serotonergic drugs. There are also at least 5 programs in the late-preclinical or clinical stage that target the disease biology, including two antisense treatments. Overall the Dravet syndrome pipeline comprises 14 drug candidates, and 9 different products have received orphan drug designations. This report reviews the state of the Dravet syndrome drug development pipeline as of July 2018 and discusses current and future opportunities.

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1. Dravet syndrome - Overview

Dravet syndrome is a neurological rare disease caused in the majority of cases by loss-of-function mutations in one copy of the SCN1A gene. Patients with Dravet syndrome fail to produce sufficient levels of functional Nav1.1 sodium channel, preventing inhibitory neurons from firing properly. As a consequence, there is an imbalance between brain excitation and inhibition that results in refractory epilepsy, intellectual disability, and behavioral and movement disorders (Dravet 2011). The mortality rate is high, with 15% of patients dying by adolescence and 20% by early adulthood (Genton et al., 2011).

For the purpose of this review we will only cover those products currently in development for the symptomatic treatment of Dravet syndrome or for the disease-modifying treatment of SCN1A-related epilepsies, but not those specifically designed to correct other gene dysfunctions that give raise to syndromes similar to Dravet.

Pharmacological management of Dravet syndrome focuses largely on the use antiepileptic drugs (Chiron 2011). Importantly, sodium channel blockers, which are often a first-line medication for the treatment of epileptic seizures, are contraindicated in Dravet syndrome and can aggravate the disease severity (Caviemans et al., 2011; Guerrini et al., 2012; de Lange et al., 2018). Most patients with Dravet syndrome are taking combinations of 3 or more antiepileptic drugs. None of these drugs alone achieves complete seizure suppression in these patients and only a minority (about 10%) of the patients are seizure-free (Lagae et al., 2018).

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