Sodium valproate injection (6 vials) and Levetiracetam injection (8 vials) encloses with all drug information sheets to serve information which health care provider need before drug administration.

Conclusion: SE BOX may be suitable for resolve the problems of SE service to reduce the waiting time and improve effectiveness of SE treatment; however the benefit of SE BOX need more study.

Keywords: status epilepticus; SE, AED

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Intranasal midazolam as initial in-hospital treatment for status epilepticus: A pharmaco-EEG cohort study

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Background: To evaluate the efficacy and tolerability of intranasal midazolam (in-MDZ) as first line in-hospital therapy in patients with status epilepticus (SE) during continuous EEG recording.

Methods: Medical records of all patients treated with in-MDZ during EEG recording between August 2015 and April 2018 were retrospectively reviewed. Data on medical history, etiology and semiology of SE, as well as anticonvulsive medication, efficacy, and safety of in-MDZ was collected. Time to end of SE regarding administration of in-MDZ and beta-band effects were independently analysed by two board certified epileptologists on EEG and with frequency analysis.

Results: In total, 42 patients (mean age 52.7 ± 22.7 years; 23 female) were treated with a median dose of 5 mg in-MDZ (range 2.5-15 mg, mean 6.4 mg, SD 2.6) for SE. Most of the patients suffered from non-convulsive status epilepticus (n = 24; 55.8%). In total, 24 (57.1%) patients were responders as SE stopped after administering in-MDZ without any other drug being given in-between. On average, SE ceased on EEG five minutes and five seconds after application of in-MDZ (median 04:56 mins; range 00:29 mins -14:53 mins; SD 03:13mins). Frequency analysis showed an increased beta-band on EEG after application of in-MDZ at four minutes and seven seconds on average (median 03:50; range 02:20 - 05:40; SD 01:09 mins). Adverse events were recorded in six patients (14.3%) with nasal irritations in five (11.9%) and prolonged sedation in one (2.6%) patient.

Conclusions: This pharmaco-EEG based study showed that in-MDZ is effective and well-tolerated for initial treatment of SE. EEG and clinical effects occur within 04:07 and 5:05 mins on average. Intranasal administration of midazolam appears to be an easily applicable and rapidly effective alternative to buccal and intramuscular application as first line treatment if an intravenous route is not available.

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Effect of ZX008 (Fenfluramine HCl Oral Solution) on Total Seizures in Dravet Syndrome

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Objective: Assess ZX008 (fenfluramine) effect on total seizure frequency in patients with Dravet syndrome.

Background: Dravet syndrome (DS) is a rare, severe, treatment-resistant, developmental epileptic encephalopathy. In a Phase 3, randomised, double-blind, placebo-controlled trial, ZX008 significantly reduced convulsive seizure (CS) frequency (defined as tonic-clonic, hemiclonic, tonic, atonic, clonic, and focal motor seizures). We present secondary analyses of total seizure (TS) frequency (defined as CS plus absence or atypical absence, myoclonic, atonic, and focal seizures without clear observable motor signs).

Methods: Patients (2-18y) with DS, and CSs not controlled by current anti-epileptic drug regimen were enrolled. Following a 6-week baseline period, patients were randomised 1:1:1 to placebo, ZX008 0.2 mg/kg/day (ZX008/0.2), or ZX008 0.8 mg/kg/day (ZX008/0.8; maximum 30 mg/day), and treated for 14 weeks, including 2-week titration. Caregivers recorded seizure number and type daily via electronic diary.

Results: A total 119 patients were randomised (10.1% UK, mean age 9 ± 4.7y). Baseline median monthly TS frequency ranged from 40.7–53.9 across groups. ZX008 significantly reduced TS frequency in a dose-related manner during 14 weeks' treatment. Median TS frequency reductions were 13.1% with placebo, 34.3% with ZX008/0.2 ($p = 0.031$), and 70.1% with ZX008/0.8 ($p < 0.001$). Median non-CS seizure subtype reductions (combined) were 55.6% with placebo and 75.1% with ZX008/0.8 ($p < 0.035$), including a 54.8 and 78.6% reduction in absence and 34.8 and 64.0% reduction in myoclonic seizures, respectively. Seizure freedom was experienced by 3 (7.5%) subjects with ZX008/0.8, 3 (7.7%) with ZX008/0.2, and none with placebo. Median longest seizure-free interval was significantly longer in ZX008 groups vs placebo. ZX008 was generally well-tolerated, and no cases of FDA-defined cardiac valvulopathy were observed; neither were there echocardiographic findings or clinical symptoms suggesting pulmonary hypertension.

Conclusions: In addition to significantly reducing convulsive seizures, ZX008/0.8 mg/kg/day also significantly reduced other

seizure types and Total seizure burden. ZX008 may represent an effective new treatment option for Dravet syndrome.

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Fenfluramine HCl Provides Long-Term Clinically Meaningful Reduction in Seizure Frequency: Results of an Open-Label Extension Study

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Introduction: Fenfluramine (FFA) has demonstrated superior efficacy compared to placebo for the reduction in frequency of convulsive seizures in children and young adults (2-18 years old) with Dravet syndrome in two recently completed Phase 3 clinical trials. Here we report the preliminary interim analysis of the effectiveness and tolerability of FFA in a long-term open label extension study.

Methods: Dravet syndrome patients completing one of the Phase 3 clinical trials were eligible to enroll in the open-label extension (OLE) study. All patients entering the OLE initiated FFA at a dose of 0.2 mg/kg/day regardless of what dose they were receiving in the core trial. After 4 weeks, the dose could be titrated up in 0.2 mg/kg/day increments up to a maximum of 0.8 mg/kg/day (max 30 mg/day; 0.5 mg/kg/day [max 20 mg/day] if patient was also on stiripentol). Effectiveness and safety were assessed at months 1, 2, and 3 and then 3-month intervals thereafter.

Results: A total of 232 patients have enrolled in the study as of March 13, 2018. A total of 128 (55.2%) were male, and the mean ± SD age was 9.1 ± 4.7 years. A total of 22 (9.5%) patients discontinued treatment: lack of efficacy (16), subject withdrawal (2), adverse event (1), death (1, SUDEP), physician decision (1), and withdrawal by caregiver (1). Median duration of treatment with FFA was 256 days (range, 58-634 days). The median percent reduction in monthly convulsive seizure frequency over the entire OLE treatment period as compared with the baseline frequency established in the core Phase 3 studies was 66.8%. A clinically meaningful reduction in convulsive seizure frequency was noted at the first observation (month 1) during OLE and continued over time (Figure). Over the entire observation period, 64.4% of patients demonstrated a 50% reduction in convulsive seizure frequency and 41.2% demonstrated a 75% reduction. At 12 months 70.4% of caregivers and 77.8% of investigators rated patients as "much improved" or "very much improved." The most common non-cardiovascular adverse events occurring in ≥10% of patients were pyrexia (21.6%), nasopharyngitis (19.4%), decreased appetite (15.9%), influenza (11.6%), diarrhoea (10.8%), and upper respiratory infection (10.3%). No patient showed echocardiographic or clinical signs of cardiac valvular heart disease or pulmonary hypertension at any time.

Conclusions: These preliminary OLE study results demonstrate FFA to provide clinically meaningful and substantial reductions in convulsive seizure frequency over time; while generally well tolerated. FFA represents a novel, highly effective antiepileptic treatment option for DS patients.

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Long-Term Cardiovascular Safety of Fenfluramine HCl in the Treatment of Dravet Syndrome: Interim Analysis of an Open-Label Safety Extension Study

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Introduction: In two recently completed Phase 3 clinical trials, fenfluramine (FFA) has demonstrated superior efficacy vs placebo for convulsive seizure reduction in children and young adults (2-18 years old) with Dravet syndrome (DS). FFA, previously marketed for weight loss, was withdrawn from the market in 1997 following reports of cardiac valvular heart disease (VHD) and pulmonary hypertension in obese adults treated with ≥60 mg/day. Here we report the cardiovascular safety findings from an interim analysis of the long-term safety extension study of low-dose FFA for DS in children and young adults.

Methods: Patients with DS who successfully completed a Phase 3 study were eligible for this open-label extension (OLE) study. Patients with current cardiac VHD, pulmonary arterial hypertension, or any degree of aortic or mitral valve regurgitation were excluded from the Phase 3 trials. All patients in the OLE were started on FFA at 0.2 mg/kg/day, after 4 weeks the dose could be titrated 0.2 mg/kg/day every 2 weeks based on effectiveness and tolerability to 0.8 mg/kg/day to maximum 30 mg/day (0.5 mg/kg/day and 20 mg/day if they were taking concurrent stiripentol). Echocardiography was performed at extension study baseline, Week 6, and 3 monthly thereafter to assess cardiac valve function and pulmonary artery pressure. Cardiac VHD was defined as