July 20, 2017

W. Charles Smithson  Carmine Boal  Gerd W. Clabaugh, Director
Secretary of the Senate  Chief Clerk of the House  Iowa Department of Public Health
State Capitol Building  State Capitol Building  Lucas Office Building
Des Moines IA 50319  Des Moines IA 50319  Des Moines IA 50319

Re: Report FY 2017- Report on Use of Medical Cannabidiol

Dear Members of the Iowa General Assembly and Director Clabaugh:

Pursuant to 2014 Iowa Acts, Chapter 1125 (SF 2360), enclosed is the report on Report on Use of Medical Cannabidiol.

If there are any questions concerning this report, please do not hesitate to contact us.

Sincerely,

Keith Saunders
Interim Executive Director
Jennifer Harbison  
Director Health Policy | Office of the Vice President for Medical Affairs  
Re: 2017 Report to the Department of Public Health and the Iowa General Assembly  

2014 Systematic Review  
A thorough systematic review of the medical literature was published in 2014 by the Cochrane Collaboration to evaluate the scientific evidence for Cannabinoids used to treat epilepsy.[1] They identified four randomized controlled studies that had used cannabinoids to treat epilepsy and these four studies had a total of 48 patients.[2-5] The systematic review stated that “No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. The dose of 200 to 300 mg daily of cannabidiol was safely administered to small numbers of patients generally for short periods of time, and so the safety of long term cannabidiol treatment cannot be reliably assessed.” There were 15 patients in the Cunha study from 1980 and they had received 200 to 300 mg of cannabidiol daily or a placebo.[3] The patients tolerated the medication for up to 4.5 months without toxicity, and 4 of the 8 who received the drug had a good response in decreasing seizures, 3 had some response and one had no improvement in seizure activity. The study by Ames in 1985 had 12 patients who received 200 to 300 mg of cannabinol daily or placebo.[2] After 4 weeks of treatment there was no difference in seizure frequency between the placebo and the treatment group. Mechoulam in 1978 had 9 patients randomized to placebo or cannabidiol.[4] Two of the four patients with cannabidiol showed some improvement in seizure control, but none of the placebo group had improvement. The fourth trial was unpublished data from 1990 by Trembly.[5] The unpublished abstract indicated that in their 12 patients no statistics had been done, but there was some improvement. One of the authors in a text book referred to this same study and said that 10 of the 12 subjects had no improvement in seizure character or frequency. Based on these four studies the authors said no reliable conclusions can be made regarding the efficacy of cannabidiol in epilepsy.  

Recent Publications and additions since the last review submitted July 2016:  
A single placebo controlled trial was published in the New England Journal of medicine by Devinsky and colleagues in May of 2017 [15]. This study took place in patients with Dravet syndrome. This was a randomized double blind placebo controlled trial in patients with Dravet syndrome between the ages of 2 and 18 years. The patients were on the cannabidiol (Epidiolex) for two weeks and following the trial were allowed to enter an open-label extension study. During the trial period, 52 cannabidiol and 56 placebo patients completed the study. Patients in the cannabidiol group had a decrease in convulsive seizures from 12.4 to 5.9 seizures per month compared to 14.9 to 14.1 convulsive seizures per month in the placebo group. The adjusted mean difference between the two groups was -22.8 percentage points with a confidence interval of -41.1 to -5.4 with a P of 0.01. Three patients became seizure free in the cannabidiol group whereas none became seizure free in the placebo group. Common side effects in this study included fatigue, decreased appetite, vomiting, and diarrhea. Out of the 108 patients eligible to enter the open label extension study, 105 patients entered.
This is the first published placebo controlled trial of cannabidiol in epilepsy. It shows that this medication is efficacious in patients with Dravet syndrome and is well tolerated.

Other published data include:

- A study of open–labelled use of cannabidiol in 48 patients with epilepsy noting an improvement in quality of life (QOLCE score) ($p<0.001$) in patients independent of decrease seizure frequency.
- A case series published in Pediatric Neurology in June of 2017 of 5 patients with Sturge-Weber syndrome noted 3 patients to have a >50% reduction in seizure frequency on cannabidiol.
- A case series published in Epilepsia in October of 2016 of 18 patients with tuberous sclerosis complex, 50% of patients at 12 months had a greater than 50% reduction in seizure frequency. 12/18 patients experienced an adverse event, most commonly drowsiness, diarrhea, and ataxia.
- A case series published in the journal of Child Neurology reported 6/7 patients with Febrile Infection Related Epilepsy Syndrome responded to Cannabidiol after failing multiple other anti-seizure medications.

These studies indicate that a similar efficacy in Dravet syndrome for pharmaceutical grade cannabidiol to other medications recently approved by the FDA for use in epilepsy. There also seems to be a broad efficacy in seizures of multiple etiologies. Cannabidiol seems to be well-tolerated with gastrointestinal (diarrhea and decreased appetite) and fatigue/sedation being the most common side effects.

**Clinical Studies Enrollment is Complete, but no published results yet:**

The following 6 studies are currently recruiting patients for epilepsy. One of the studies is from the last year’s list of studies in progress and they have completed the study, but the results are not yet published. There are an additional 5 studies that have completed, but the results are not yet available.

**Study 1:**
- **Title:** A Randomized Controlled Trial to Investigate Possible Drug-drug Interactions Between Clobazam and Cannabidiol
- **Recruitment:** Completed
- **Study Results:** Results are being analyzed, but not yet available.
- **Conditions:** Epilepsy
- **Interventions:** Drug: Placebo|Drug: GWP42003-P
- **URL:** [https://ClinicalTrials.gov/show/NCT02565108](https://ClinicalTrials.gov/show/NCT02565108)

**Study 2:**
- **Title:** A Dose-ranging Pharmacokinetics and Safety Study of GWP42003-P in Children With Dravet Syndrome (GWPCARE1)
- **Recruitment:** Completed
- **Study Results:** No Results Available
- **Conditions:** Epilepsy|Dravet Syndrome
- **Interventions:** GWP42003-P|Drug: Placebo control
- **URL:** [https://ClinicalTrials.gov/show/NCT02091206](https://ClinicalTrials.gov/show/NCT02091206)

**Study 3:**
- **Title:** A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults
- **Recruitment:** Completed
- **Study Results:** No Results Available
- **Conditions:** Epilepsy|Lennox-Gastaut Syndrome
- **Interventions:** GWP42003-P|Drug: Placebo Control
- **URL:** [https://ClinicalTrials.gov/show/NCT02224690](https://ClinicalTrials.gov/show/NCT02224690)
Study 4:
- Title: A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults
- Recruitment: Completed
- Study Results: No Results Available
- Conditions: Epilepsy|Lennox-Gastaut Syndrome
- Interventions: GWP42003-P|Drug: Placebo control
- URL: https://ClinicalTrials.gov/show/NCT02224560

Study 5:
- Title: Antiepileptic Efficacy Study of GWP42003-P in Children and Young Adults With Dravet Syndrome (GWPCARE1)
- Recruitment: Completed
- Study Results: No Results Available
- Conditions: Epilepsy|Dravet Syndrome
- Interventions: Drug: GWP42003-P|Drug: Placebo control
- URL: https://ClinicalTrials.gov/show/NCT02091375

Study 6:
- Title: Cannabidiol Oral Solution in Pediatric Participants With Treatment-resistant Seizure Disorders
- Recruitment: Completed
- Study Results: Has Results
- Conditions: Seizures
- Interventions: Drug: Cannabidiol Oral Solution
- URL: https://ClinicalTrials.gov/show/NCT02324673

**Clinical Studies Currently Being Conducted**

Study List: The first 8 studies in this list are currently recruiting patients for epilepsy and were on the list of 11 studies from last year. Many of these 8 studies are scheduled to be completed within the next 12 months. There are an additional 14 studies that are now being conducted since last year.

Study 1:
- Title: Epidiolex and Drug Resistant Epilepsy in Children
- Recruitment: No Results Available
- Conditions: Epilepsy
- Interventions: Drug: Cannabidiol (Epidiolex)
- URL: https://ClinicalTrials.gov/show/NCT02397863

Study 2:
- Title: Cannabidiol (CBD) and Pediatric Epilepsy
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epilepsy
- Interventions: Cannabidiol | Tetrahydrocannabinol
- URL: https://ClinicalTrials.gov/show/NCT02447198

Study 3:
- Title: Genetic Analysis Between Charlotte's Web Responders Versus Non-Responders in a Dravet Population
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Dravet Syndrome
- Interventions:
- URL: [https://ClinicalTrials.gov/show/NCT02229032](https://ClinicalTrials.gov/show/NCT02229032)

Study 4:
- Title: An Open-label Extension Trial to Investigate Possible Drug-drug Interactions Between Stiripentol or Valproate and Cannabidiol in Patients With Epilepsy
- Recruitment: Not yet recruiting
- Study Results: No Results Available
- Conditions: Epilepsy
- Interventions: Drug: GWP42003-P
- URL: [https://ClinicalTrials.gov/show/NCT02607904](https://ClinicalTrials.gov/show/NCT02607904)

Study 5:
- Title: A Randomized Controlled Trial to Investigate Possible Drug-drug Interactions Between Stiripentol or Valproate and Cannabidiol in Patients With Epilepsy
- Recruitment: Not yet recruiting
- Study Results: No Results Available
- Conditions: Epilepsy
- Interventions: Drug: GWP42003-P|Drug: Placebo
- URL: [https://ClinicalTrials.gov/show/NCT02607891](https://ClinicalTrials.gov/show/NCT02607891)

Study 6:
- Title: A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet Syndrome
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epilepsy|Dravet Syndrome
- Interventions: Drug: GWP42003-P|Drug: Placebo Control
- URL: [https://ClinicalTrials.gov/show/NCT02224703](https://ClinicalTrials.gov/show/NCT02224703)

Study 7:
- Title: An Open-label Extension Trial to Investigate Possible Drug-drug Interactions Between Clobazam and Cannabidiol
- Recruitment: Not yet recruiting
- Study Results: No Results Available
- Conditions: Epilepsy
- Interventions: Drug: GWP42003-P
- URL: [https://ClinicalTrials.gov/show/NCT02564952](https://ClinicalTrials.gov/show/NCT02564952)

Study 8:
- Title: A Randomized Controlled Trial of Cannabidiol (GWP42003-P, CBD) for Seizures in Tuberous Sclerosis Complex.
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Tuberous Sclerosis Complex|Seizures
- Interventions: Drug: GWP42003-P|Drug: Placebo
- URL: [https://ClinicalTrials.gov/show/NCT02544763](https://ClinicalTrials.gov/show/NCT02544763)

Study 9:
- Title: Cannabidiol (CBD) to 27 Patients (Aged 2 Years - 19 Years) With Drug Resistant Epilepsy
- Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Epilepsy
Interventions: Drug: Cannabidiol
URL: https://ClinicalTrials.gov/show/NCT02286986

Study 10:
Title: Cannabidiol Oral Solution as an Adjunctive Treatment for Treatment-resistant Seizure Disorder
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Seizures
Interventions: Drug: Cannabidiol Oral Solution
URL: https://ClinicalTrials.gov/show/NCT02318602

Study 11:
Title: Cannabidiol Oral Solution for Treatment of Refractory Infantile Spasms
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Spasms, Infantile
Interventions: Drug: Cannabidiol Oral Solution
URL: https://ClinicalTrials.gov/show/NCT02551731

Study 12:
Title: Cannabinoid Therapy for Pediatric Epilepsy
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Epilepsy
Interventions: Drug: TIL-TC150
URL: https://ClinicalTrials.gov/show/NCT02983695

Study 13:
Title: Expanded Use of Cannabidiol Oral Solution
Recruitment: Available
Study Results: No Results Available
Conditions: Refractory Epilepsy
Interventions: Drug: Cannabidiol oral solution
URL: https://ClinicalTrials.gov/show/NCT03196934

Study 14:
Title: Safety and Tolerability of Cannabidiol in Subjects With Drug Resistant Epilepsy
Recruitment: Available
Study Results: No Results Available
Conditions: Epilepsy
Interventions: Drug: Cannabidiol
URL: https://ClinicalTrials.gov/show/NCT02660255

Study 15:
Title: Treatment of Drug Resistant Epilepsy
Recruitment: Available
Conditions: No Results Available
Conditions: Epilepsy
Interventions: Drug: cannabidiol|Other: Blood Test
URL: https://ClinicalTrials.gov/show/NCT02461706
Study 16:
- Title: An Open Label Extension Study of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet or Lennox-Gastaut Syndromes
- Recruitment: Enrolling by invitation
- Study Results: No Results Available
- Conditions: Epilepsy|Dravet Syndrome|Lennox-Gastaut Syndrome
- Interventions: Drug: GWP42003-P
- URL: https://ClinicalTrials.gov/show/NCT02224573

Study 17:
- Title: An Open-label Extension Trial of Cannabidiol (GWP42003-P, CBD) for Seizures in Tuberous Sclerosis Complex (GWPCARE6)
- Recruitment: Enrolling by invitation
- Study Results: No Results Available
- Conditions: Tuberous Sclerosis Complex|Seizures
- Interventions: Drug: GWP42003-P
- URL: https://ClinicalTrials.gov/show/NCT02544750

Study 18:
- Title: A Study to Evaluate the Safety, Tolerability and Efficacy of Oral Administration of PTL101 (Cannabidiol) as an Adjunctive Treatment for Pediatric Intractable Epilepsy
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epilepsy Intractable
- Interventions: Drug: PLT101
- URL: https://ClinicalTrials.gov/show/NCT02987114

Study 19:
- Title: Cannabidiol in Children With Refractory Epileptic Encephalopathy
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epileptic Encephalopathy
- Interventions: Drug: CanniMed® 1:20
- URL: https://ClinicalTrials.gov/show/NCT03024827

Study 20:
- Title: Phase 3 Trial of Cannabidiol (CBD; GWP42003-P) for Infantile Spasms: Open-label Extension Phase (GWPCARE7)
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Infantile Spasms
- Interventions: Drug: GWP42003-P
- URL: https://ClinicalTrials.gov/show/NCT02954887

Study 21:
- Title: Trial of Cannabidiol (CBD; GWP42003-P) for Infantile Spasms (GWPCARE7)
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Infantile Spasms
- Interventions: Drug: GWP42003-P
- URL: https://ClinicalTrials.gov/show/NCT02953548
Study 22:
- Title: University of Alabama at Birmingham (UAB) Adult CBD Program
- Recruitment: Recruiting
- Study Results: No Results Available
- Conditions: Epilepsy|Seizures
- Interventions: Drug: Epidiolex
- URL: https://ClinicalTrials.gov/show/NCT02700412

References


26. Rosenberg EC, Louik J, Conway E, Devinsky O, Friedman D. Quality of Life in Childhood Epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. Epilepsia. 2017 Jun 15


Sincerely,

Ronald A. Herman
Dr. Ron Herman PhD
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ADDENDUM notification:

This report has been addended by myself to reflect new knowledge in the field of cannabidiol and epilepsy. Additions include recent publications and additions occurred after July of 2016, an update from the US NIH in regards to ongoing clinical trials, and updated references.

Sincerely,

Michael Ciliberto, MD
Assistant Professor
Division of Pediatric Neurology
Stead Family Department of Pediatrics
University of Iowa Children’s Hospital