ZAVESCA® (miglustat)
Reformulation of ZAVESCA

SUMMARY

- The administration of reformulated ZAVESCA capsules (orally or via an enteral tube) has not been formally assessed at this time. Therefore, the decision to reformulate ZAVESCA for the purpose of administration via alternative routes (i.e., in liquid, orally, or via nasogastric tube) is at the discretion of the prescribing physician.
- A stability study found that a mixture of the contents of a ZAVESCA capsule and D-mannitol could be stored for 8 weeks at 30°C and 65% relative humidity, without a significant decrease in the amount of unchanged miglustat.[1]
- Several published studies report details regarding extemporaneous compounding of miglustat solution or suspension prepared from the contents of opened ZAVESCA capsules.[2-4] Additionally, 1 prospective study and 2 case reports describe ZAVESCA administration via an enteral feeding tube (nasogastric or gastrostomy tube) in pediatric patients.[3,5,6]
- A search of the scientific literature identified 1 publication that describes the stability of miglustat dissolved in InOrpha® suspending vehicle, a liquid suspending excipient for compounding of oral solutions and suspensions.[7]

CLINICAL DATA

Internal Data

A study was conducted to determine the stability of miglustat after ZAVESCA capsules were opened and the ZAVESCA powder mixed with D-mannitol. The dry mixture was stored in opened and closed scintillation vials, at room temperature and in a controlled environment with 30°C and 65% humidity. The study concluded that the miglustat in a dry mixture of ZAVESCA powder with D-mannitol stored for up to 8 weeks, at 30°C and 65% humidity, is expected to be stable.[1]

Extemporaneous Compounding Experience

There are no internal data regarding extemporaneously compounded miglustat solution or suspension prepared from the contents of opened ZAVESCA capsules. With an aqueous solubility in water >1000 mg/mL as a free base at ambient temperature, ZAVESCA is highly soluble.[8]

Information From the Scientific Literature

A study reported the pharmacokinetics of miglustat administered as single- and multiple-doses in pediatric patients with GM2 gangliosidosis (N=11). The drug dose was adjusted as per each patient's body surface area (BSA): BSA <0.8 m^2, 50-90 mg three times a day (TID); BSA 0.8-1.3 m^2, 100 mg TID; BSA >1.3 m^2, 200 mg TID. Juvenile patients swallowed the normal 100 mg miglustat capsules, whereas infantile patients had the drug compounded to a powder, weighed by the investigational pharmacy, and placed in packets. Parents then dissolved the appropriate amount of drug from the packets in an aqueous solution just before administration by mouth or gastrostomy.[2] In a prospective, open-label study conducted among French pediatric patients with Niemann-Pick disease type C (N=20), commercially available miglustat 100 mg capsules were repackaged into smaller capsules of 50 mg to facilitate easier swallowing for 1 of the study patients.[3] A case report described the experience of a 12-month treatment with an individual formulation of miglustat in a pediatric patient with GM1 gangliosidosis. Personalized capsules (for hospital and home administration) were prepared, with different doses (from 30 mg per day-210 mg/day in 3 doses), using ZAVESCA and mannitol, as excipient, considering lactose is to be avoided in GM1 gangliosidosis.[4]

Although ZAVESCA has a bitter taste that patients may find intolerable without the masking effect of flavorings and sweeteners, to reduce the risk of gastrointestinal side effects associated with ZAVESCA, drinks containing added sugar, sorbitol or mannitol, as well as milk (unless lactose-free), should still be avoided.[9]

Bioavailability

The bioavailability of miglustat when administered orally in the form of capsules has been compared with that of miglustat when administered orally as a solution in a randomized, open-label, single dose, crossover study in 24 healthy volunteers. Each subject received 3 oral doses of miglustat (100 mg capsule in a fasted state, 100 mg capsule in a fed state, 100 mg solution, prepared in water, in a fasted state) in a random order with a washout period of at least 6 days between each dose. Blood samples for pharmacokinetic analysis were taken pre-dose and at intervals up to 36 hours after each dose. The mean oral bioavailability of a 100 mg miglustat is about 97% relative to an oral solution administered under fasting conditions.[8,10]

Administration Via an Enteral Feeding Tube

Information From the Scientific Literature

One prospective study and 2 case reports described ZAVESCA administration via an enteral feeding tube (nasogastric or gastrostomy tube) in pediatric patients.[3,5,6]

Stability

Information From the Scientific Literature

One publication that describes the stability of miglustat dissolved in InOrpha® suspending vehicle, a liquid suspending excipient for compounding of oral solutions and suspensions, was identified. The authors report the contents of ZAVESCA 100 mg capsules (a powder blend comprising miglustat and several excipients) were transferred into InOrpha®. Although miglustat was soluble in InOrpha® at all concentrations tested, some of the excipients were not. An InOrpha® suspension containing 20 mg/mL miglustat was investigated initially. Subsequently, a pH-adjusted suspension of 20 mg/mL, and non-adjusted 10 and 5 mg/mL suspensions were evaluated. All suspensions were stored under refrigerated conditions. Physicochemical and microbiological challenge testing was performed at 0 hours and after 14 and 28 days. Degradation was assessed by high-performance liquid chromatography, appearance was assessed visually, and pH was recorded. Additionally, suspensions were inoculated with seven species of bacteria, yeast, and mold, and growth evaluated using membrane filtration. Miglustat 20 mg/mL suspension changed from yellow (0 hours) to brown (days 14 and 28); pH remained stable at 7.4-7.6. Pure InOrpha® (pH 4.6) remained yellow throughout the study. Pure InOrpha® adjusted to pH 7.5 displayed a brownish discoloration after 9 days. Miglustat 5 and 20 mg/mL suspensions, adjusted to pH 6.5 and 4.4, respectively, remained yellow at days 14 and 28. Miglustat 10 mg/mL suspension (pH 7.3) changed from yellow to brown on day 9. No degradates were detected for any of the concentrations tested. There was no proliferation of microorganisms over the study period; in all cases the level of contamination was reduced.[7]

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, DERWENT® (and/or other resources, including internal/external databases) was conducted on 28 February 2024.

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