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ORIGINAL RESEARCH

Stability of refrigerated miglustat after preparation in InOrpha® flavored suspending excipient for compounding of oral solutions and suspensions

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Background: Miglustat (Zavesca®) is an oral treatment for type 1 Gaucher disease and Niemann–Pick disease type C. Patients with Niemann–Pick disease type C often have difficulties swallowing, and miglustat has an unpleasant taste. The stability of miglustat at 2°C–8°C prepared in InOrpha® suspending vehicle, a liquid taste-masking agent, was assessed.

Methods: 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. Suspensions were inoculated with seven species of bacteria, yeast, and mold, and growth evaluated using membrane filtration.

Results: 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 clearly reduced.

Conclusion: InOrpha® suspensions containing miglustat 5 mg/mL (without pH adjustment) and 20 mg/mL (with pH adjusted to 4.4) display stable physicochemical and microbiological properties over 28 days.

Keywords: microbiological challenge, Niemann–Pick disease type C, type 1 Gaucher disease

Introduction

Miglustat (Zavesca® 100 mg hard gelatine capsules; Actelion Pharmaceuticals Ltd, Allschwil, Switzerland) is used to treat mild to moderate type 1 Gaucher disease (GD1) when enzyme replacement therapy is unsuitable, and Niemann–Pick disease type C (NP-C), which are both inherited metabolic disorders.[1–4] The standard adult miglustat dose for GD1 is 100 mg three times a day. For NP-C, the standard dose for adults and adolescents is 200 mg three times a day and for patients under the age of 12 the dose should be adjusted on the basis of body surface area.[1]

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Glycosphingolipid lysosomal storage disorders, such as GD1, arise as a result of deficiencies of the enzymes responsible for the catabolism of glycosphingolipids.[5] GD1 is a rare inherited metabolic disorder caused by a failure to degrade glucosylceramide, resulting in lysosomal storage of this material and widespread pathology. The inhibitory action of miglustat on glucosylceramide synthase forms the rationale for substrate reduction therapy in GD1. NP-C is a rare, invariably progressive, and eventually fatal neurodegenerative disorder characterized by impaired intracellular lipid trafficking leading to glycosphingolipid accumulation in neuronal and glial cells without any particular defect in catabolic enzymes. The resulting pathological lysosomal accumulation of these glycolipids has widespread clinical consequences. Through its action as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase and its ability to cross the blood–brain barrier, miglustat can reduce the amount of glucosylceramide formed in the brain, and subsequently reduce the neurotoxic accumulation of more complex glycosphingolipids.[5,6]

Miglustat (1,5 [butylimino]-1,5-dideoxy-D-glucitol) is a single stereoisomer synthetically derived from an imino sugar extracted from plants and microorganisms. It has a molecular weight of 219 and is a white crystalline substance that is highly soluble in water (>1 g/mL at ambient temperature).[7]

InOrpha® (Inresa Pharma, Bartenheim, France) is a liquid suspending excipient for compounding of oral solutions and suspensions that is free from sugar, alcohol, and paraben. It contains a noncarcinogenic sweetener, sucralose, as well as a caramel flavor agent and a taste-masking agent. It has successfully been used as a suspending vehicle for hydrocortisone[8] and melatonin.[9] The aim of this study was to evaluate the stability of miglustat preparations when dissolved in InOrpha® suspending vehicle with regard to physicochemical and microbiological properties.

Methods

First stability study

Physicochemical testing

Miglustat 20 mg/mL suspension was prepared by transferring the contents of one Zavesca 100 mg capsule per 5 mL of InOrpha® suspending vehicle (Inresa Pharma). The resulting suspension was thoroughly shaken to ensure complete dissolution of miglustat. A volume of 100 mL of suspension was kept in a 100 mL glass volumetric flask and stored under refrigerated conditions at 2°C–8°C. To serve as a blank, 100 mL of pure InOrpha® suspending vehicle in a 100 mL glass volumetric flask was stored under the same conditions.

Degradation of miglustat suspension at 0 hours and after 14 and 28 days was assessed via high-performance liquid chromatography (HPLC) using an Agilent 1100 system with a single wavelength detector set to 208 nm (Agilent Technologies, Santa Clara, CA, USA). Chromatographic separation was achieved on a Waters X-Bridge Amide HPLC column (150 mm ×2.1 mm, 3.5 µm particle size; Waters Corporation, Milford, MA, USA) using a mobile phase consisting of 10% ammonium acetate buffer/90% acetonitrile (both reagents from Sigma-Aldrich Co, St Louis, MO, USA) at an isocratic flow rate of 0.8 mL/min. Prior to analysis, 5 mL miglustat suspension was diluted with 95 mL of mobile phase to give a final concentration of 1 mg/mL of miglustat. An aliquot was filtered through a 0.45 µm PTFE syringe filter (AIT, Houilles, France) prior to injection into the high-performance liquid chromatograph. The injection volume was 10 µL, the autosampler temperature was 20°C, and the column temperature was 40°C. Miglustat reference standard (Actelion Pharmaceuticals Ltd) was used to validate the following method parameters: selectivity (no interferences from known degradates and excipients), linearity (R^2=0.9999 for 50%–200% method concentration, n=6), repeatability (0.3% relative standard deviation for injections at 100% method concentration, n=6), reference solution stability (24 hours at ambient room temperature), limit of detection (0.03% of method concentration), and limit of quantification (0.10% of method concentration).

The appearance of miglustat 20 mg/mL suspension and pure InOrpha® suspending vehicle was assessed by manual visual inspection in both 50 mL glass volumetric flasks and 50 mL polypropylene tubes (Sarstedt AG, Nümbrecht, Germany) at 0 hours and after 14 and 28 days. The pH at each of these time points was measured using a Uniprobe Pt 1000 glass electrode (Metrohm, Zolfingen, Switzerland). Following the results of appearance testing, follow-up experiments were conducted where the pH of the pure InOrpha® suspending vehicle was adjusted to be the same as that of the miglustat 20 mg/mL suspension, ie, pH 7.5.

Microbiological challenge testing

All microbial testing was performed by Compliance GmbH (Cologne, Germany). Miglustat 20 mg/mL suspension was again prepared by dissolving the contents of one Zavesca 100 mg capsule per 5 mL of InOrpha® suspending vehicle. Microorganisms used were the bacteria *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC 8739, and *Pseudomonas chlororaphis* DSM 6698; the yeasts *Candida albicans* ATCC 10231, and *Zygosaccharomyces rouxii* NCYC 381; and the

mold *Aspergillus brasiliensis* ATCC 16404. *P. chlororaphis* was purchased from Leibniz Institute DSMZ – German Collection of Microorganisms and Cell Cultures (Braunschweig, Germany), *Z. rouxii* from National Collection of Yeast Cultures (NCYC) (Norwich, UK), and all other organisms from American Type Culture Collection (ATCC) (Manassas, VA, USA). The cultures were prepared as per manufacturer's instructions and used within 24 hours of preparation.

Prior to stability testing, the suitability of the microbiological challenge testing method was verified according to European Pharmacopoeia Edition 8 Chapter 2.6.12[10] to ensure that detection of <100 colony forming units (cfu) was possible. For this, 1 mL of miglustat 20 mg/mL suspension was pipetted into 9 mL of sodium chloride-peptone buffer. After vortexing, the pH values were recorded to ensure they were between pH 6 and 8. The samples were then inoculated with $\leq 1\times10^2$ cfu/mL of each microorganism (one sample per organism). Samples of sodium chloride-peptone buffer were also inoculated with microorganisms to serve as a reference. Membrane filtration was performed for each sample using a stainless steel filtration unit and cellulose nitrate filters (Sartorius AG, Göttingen, Germany). Filters were washed three times with 100 mL of sodium chloride-peptone buffer. The filters were then put on agar plates as follows: casein-soya-peptone agar and incubation for 2 days at 32.5°C±2.5°C for *S. aureus*, *P. aeruginosa*, and *E. coli*; and casein-soya-peptone agar and incubation for 2 days at 22.5°C±2.5°C for *P. chlororaphis*. For yeasts and molds, the filters were put on Sabouraud agar and incubated for 5 days at 22.5°C±2.5°C. In addition, control miglustat samples were prepared, filtered, and incubated as described but without being inoculated with microorganisms to verify the absence of any microbial contamination in the test articles.

Microbial proliferation risk of the miglustat suspensions was tested using low-level inoculum and a brief daily exposure to air to simulate conditions of possible contamination during the preparation of the suspension or during its use. The concentration of each microorganism inoculum was adjusted to yield approximately 5×10^4 cfu/mL. From this, 50 µL was added to 4.95 mL of miglustat 20 mg/mL suspension to reach 10^2 to 10^3 cfu/mL. All samples were then stored under refrigerated conditions at 2°C–8°C. Everyday the samples were taken out of the refrigerator and opened for approximately 10 seconds. The microbial counts of the inoculum at 0 hours and at 14 and 28 days were determined by the membrane filtration method, as described above for the suitability test. Microbial growth was considered evident when the microbial population increased by >0.5 $\log_{10}$ compared with the precedent inoculum count.

Second stability study

A second stability test study was conducted following the results of the first stability study to investigate the stability of lower concentrations of miglustat suspension at 5 mg/mL and 10 mg/mL. In addition, the effect of adjusting the pH of miglustat 20 mg/mL suspension to 4.4, ie, similar to the pH of pure InOrpha® suspending vehicle, was examined.

Miglustat 20 mg/mL suspension pH 4.4 was prepared as per the first stability test study and an additional 2.5 g of citric acid (Sigma-Aldrich Co) was added to 100 mL miglustat suspension (Sigma-Aldrich Co). Miglustat 10 mg/mL suspension was prepared by dissolving the contents of one Zavesca 100 mg capsule per 10 mL of InOrpha® suspending vehicle. Miglustat 5 mg/mL suspension was prepared by dissolving the contents of one Zavesca 100 mg capsule per 20 mL of InOrpha® suspending vehicle.

Physicochemical testing was conducted as described above for each of these suspensions. Microbiological challenge testing was conducted as described above but only for the miglustat 20 mg/mL suspension adjusted to pH 4.4 and for the miglustat 5 mg/mL suspension.

Results

First stability test study

Physicochemical testing

No degradates were detected for the miglustat 20 mg/mL suspension after 28 days of refrigerated storage at 2°C–8°C versus at 0 hours.

The appearance of miglustat 20 mg/mL suspension compared with pure InOrpha® suspending vehicle at 0 hours was similar, both being yellowish, turbid, and slightly viscous. Although no degradation could be detected, miglustat 20 mg/mL suspension was brown after 14 and 28 days of refrigerated storage. In contrast, there was no change in the appearance of InOrpha® suspending vehicle over time. The pH of miglustat 20 mg/mL suspension at 0 hours and after 14 and 28 days refrigerated storage was 7.4, 7.6, and 7.4, respectively. Pure InOrpha® suspending vehicle had a lower pH of 4.7, 4.9, and 4.7, respectively, at these time points. When the pH of pure InOrpha® suspending vehicle was adjusted to 7.5 to match that of the miglustat 20 mg/mL suspension, a brownish discoloration became visible after 9 days. The appearance of either miglustat 20 mg/mL suspension or pure InOrpha® suspending vehicle at each time point tested was not dependent on the storage vessel being glass or plastic, ie, the discoloration of miglustat 20 mg/mL after 14 and 28 days was visible in both glass and plastic storage vessels.

Microbiological challenge testing

The suitability test of the methodology for microbial testing confirmed that the method was suitable for the intended application as the recovery for all microorganisms in the miglustat suspensions was within 50%–200% of the corresponding sodium chloride-peptone reference sample. In addition, no microorganisms were detected in the noninoculated control miglustat suspensions, demonstrating the absence of microbiological contamination of the test items.

Table 1 summarizes the log-numbers of the microorganisms tested for miglustat 20 mg/mL suspension. For *S. aureus*, *P. aeruginosa,* and *E. coli*, a 3-log reduction was found after 14 days and no increase was found after 28 days. For *P. chlororaphis*, a 0.41-log increase was found after 14 days compared with at 0 hours, and a 1.33-log reduction was found after 28 days compared with the 14-day time point. There was a 0.75-log reduction for *C. albicans* after 14 days and no cfus found after 28 days. A 1.44-log reduction was found for *Z. rouxii* after 14 days and no cfus after 28 days. *A. brasiliensis* was not reduced after 14 days but did show a 0.96-log reduction after 28 days compared with at 14 hours.

Second stability test study

Physiochemical testing

The appearances of miglustat 20 mg/mL suspension adjusted to pH 4.4, miglustat 10 mg/mL suspension, miglustat 5 mg/mL suspension, and pure InOrpha® suspending vehicle at 0 hours were all similar, namely yellowish, turbid, and slightly viscous. After 14 days storage under refrigerated conditions, the miglustat 10 mg/mL suspension had turned brownish (onset of change occurring 9 days after storage).

However, miglustat 5 mg/mL suspension, miglustat 20 mg/mL adjusted to pH 4.4, and pure InOrpha® suspending vehicle remained yellow. A similar observation was made after 28 days, with the miglustat 10 mg/mL having a darker brown color than after 14 days. The other miglustat suspensions and pure InOrpha® suspending vehicle remained yellow. The pH of miglustat 20 mg/mL suspension adjusted to pH 4.4 remained at 4.4 after 14 and 28 days. For miglustat 10 mg/mL, the pH was 7.0 at 0 hours and 7.3 after 14 and 28 days. For miglustat 5 mg/mL, the pH was 6.3 at 0 hours and 6.5 after 14 and 28 days. The pH of pure InOrpha® suspending vehicle was 4.7 at 0 hours and 4.7 and 4.9 after 14 and 28 days, respectively. No degradation was observed for any of the suspensions when tested by HPLC (see Figure 1 showing example chromatograms after 0 hours and 28 days for the 20 mg/mL suspension).

Table 1 Microbiological challenge testing of miglustat 20 mg/mL in InOrpha® suspending vehicle over time (cfu/mL expressed as log_{10}-numbers)

Microorganism	Inoculum	Time interval		
		0 hours	14 days	28 days
Staphylococcus aureus	3.42	2.94	0	0
Pseudomonas aeruginosa	3.15	3.15	0	0
Escherichia coli	2.19	3.66	0	0
Pseudomonas chlororaphis	2.97	3.60	4.01	2.68
Candida albicans	2.54	2.51	1.76	0
Zygosaccharomyces rouxii	2.59	2.48	1.04	0
Aspergillus brasiliensis	2.33	2.54	2.52	1.56

Microbiological challenge testing

Table 2 summarizes the log-numbers of the microorganisms tested for miglustat 20 mg/mL in InOrpha® suspending vehicle adjusted to pH 4.4. For all bacteria, a reduction to the limit of detection of <1 cfu/mL (ie, 0 log number) was reached within 14 days and no increase was observed after 28 days. For *C. albicans*, a reduction to <5 cfu/mL was reached within 14 days followed by further reduction to the limit of detection of <1 cfu/mL after 28 days. A 1.76-log reduction was found for *Z. rouxii* after 14 days and a reduction to the limit of detection of <1 cfu/mL was reached after 28 days. *A. brasiliensis* showed a 1.54-log reduction after 14 days and a reduction to the limit of detection was reached after 28 days.

Table 3 summarizes the log-numbers of the microorganisms tested for miglustat 5 mg/mL in InOrpha® suspending vehicle. For *S. aureus*, *P. aeruginosa*, and *E. coli*, a reduction to the limit of detection of <1 cfu/mL was reached within 14 days and no increase was observed after 28 days. For *P. chlororaphis*, a reduction to <5 cfu/mL was reached within 14 days with further reduction to <1 cfu/mL after 28 days. A 0.31-log reduction was observed for *C. albicans* after 14 days and a 1.45-log reduction was observed after 28 days compared with the at 14 days. For *Z. rouxii*, a reduction to <5 cfu/mL was reached within 14 days with further reduction to <1 cfu/mL after 28 days. *A. brasiliensis* showed a 0.51-log reduction after 14 days and a further 1.78-log reduction after 28 days.

The test was also performed for pure InOrpha® suspending vehicle (data not shown). For *S. aureus*, *P. aeruginosa*, *E. coli*, and *Z. rouxii*, a reduction to the limit of detection of <1 cfu/mL was reached within 14 days and no increase was observed after 28 days. For *P. chlororaphis* and *C. albicans*, a reduction to 5 cfu/mL was reached within 14 days and no increase was observed after 28 days. *A. brasiliensis* showed a 0.78-log reduction after 14 days and a reduction to the limit of detection of <1 cfu/mL was reached within 28 days.

The three microbial studies demonstrate that none of the microorganisms tested showed any growth over the period of 28 days when stored under refrigerated conditions.

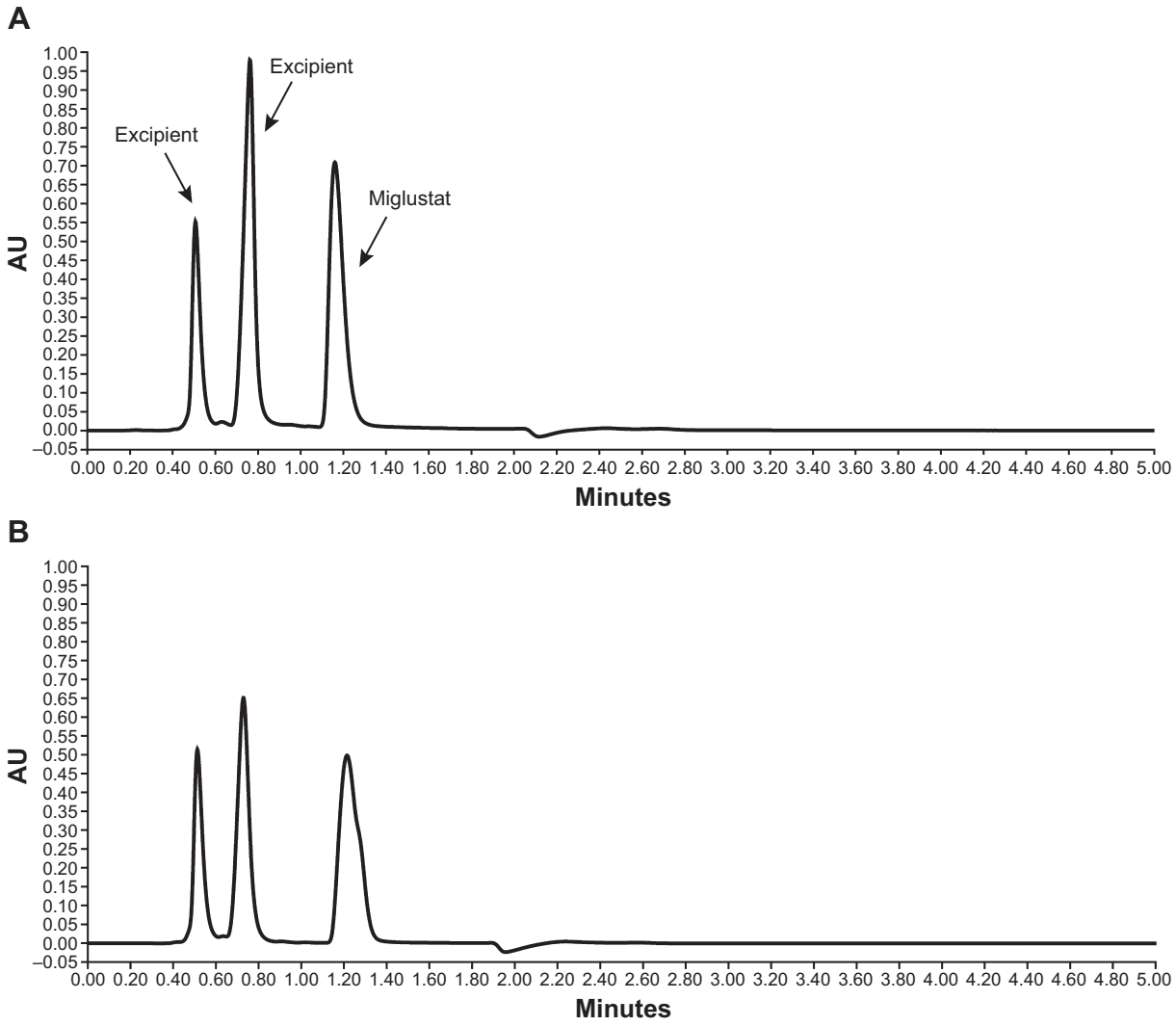

Figure 1 Chromatograms of 20 mg/mL miglustat in InOrpha® suspension at (**A**) 0 hours and (**B**) after 28 days at 2°C–8°C.

Furthermore, all organisms tested were reduced by at least 97% after 28 days.

Discussion

The presented results suggest that miglustat 5 mg/mL in InOrpha® suspension and miglustat 20 mg/mL in InOrpha® suspension adjusted to pH 4.4 with citric acid are stable with regard to their physicochemical and microbiological properties when stored and refrigerated (2°C–8°C) over the period of 4 weeks (28 days).

Based on HPLC analysis, there appears to be no degradates when miglustat is suspended in InOrpha® suspending vehicle.

Table 2 Microbiological challenge testing of miglustat 20 mg/mL in InOrpha® suspending vehicle adjusted to pH 4.4 over time (cfu/mL expressed as $\log_{10}$-numbers)

Microorganism	Inoculum	Time interval		
		0 hours	14 days	28 days
Staphylococcus aureus	2.66	2.35	0	0
Pseudomonas aeruginosa	3.25	<0.7	0	0
Escherichia coli	3.18	3.29	0	0
Pseudomonas chlororaphis	3.02	<0.7	0	0
Candida albicans	2.60	2.75	<0.7	0
Zygosaccharomyces rouxii	2.50	2.46	<0.7	0
Aspergillus brasiliensis	2.48	2.54	1.00	0

Table 3 Microbiological challenge testing of miglustat 5 mg/mL in InOrpha® suspending vehicle (cfu/mL expressed as $\log_{10}$-numbers)

Microorganism	Inoculum	Time interval		
		0 hours	14 days	28 days
Staphylococcus aureus	2.66	2.69	0	0
Pseudomonas aeruginosa	3.25	2.40	0	0
Escherichia coli	3.18	2.30	0	0
Pseudomonas chlororaphis	3.02	2.62	<0.7	0
Candida albicans	2.60	2.71	2.40	0.95
Zygosaccharomyces rouxii	2.50	2.56	0.7	0
Aspergillus brasiliensis	2.48	2.57	2.08	0.30

A brownish discoloration of miglustat 10 mg/mL and 20 mg/mL suspensions became evident after 9 days of refrigerated storage. This discoloration seemed to be a result of the higher pH of the 10 mg/mL and 20 mg/mL as it was not evident at the 5 mg/mL concentration or when miglustat 20 mg/mL suspension was adjusted to a similar pH of pure InOrpha® suspending vehicle, ie, pH 4.4. Moreover, increasing the pH of pure InOrpha® suspending vehicle by addition of sodium hydroxide also resulted in a brownish appearance after 9 days, suggesting that one or more excipients of the suspending vehicle undergo a change when exposed to a higher pH. It is not clear which excipient/excipients is/are responsible.

The microorganisms tested in this study represent a broad spectrum of potential manufacturing, nosocomial, and household contaminants, including gram-negative and gram-positive bacteria, common yeasts, and molds, as recommended per the European Pharmacopeia chapter 5.1.3[11] for oral applications for antimicrobial effectiveness test. In addition, the sugar tolerant yeast *Z. rouxii*, which is recommended for antimicrobial testing if carbohydrate concentrations are high, and the psychrotolerant ("refrigerator"-tolerant) bacterium *P. chlororaphis* were included. The results from the microbiological challenge testing of all miglustat suspensions show that, when challenged with a low level of contamination by microorganisms, there was no proliferation in miglustat in InOrpha® suspending vehicle. It should be noted that InOrpha® suspending vehicle does contain a preservative.

Conclusion

In conclusion, miglustat 5 mg/mL in InOrpha® suspension and miglustat 20 mg/mL in InOrpha® suspension adjusted to pH 4.4 appear to be stable with regard to their physicochemical and microbiological properties for 28 days under refrigerated conditions.

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Disclosure

All authors are employees of Actelion Pharmaceuticals Ltd, Allschwil, Switzerland, the manufacturers of miglustat. The authors report no other conflicts of interest in this work.

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