



HAUTE AUTORITÉ DE SANTÉ

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**TRANSPARENCY COMMITTEE**

OPINION

16 December 2009

**ZAVESCA 100 mg, capsules**  
**B/84 (CIP: 564 116-9)**

**Applicant: ACTELION PHARMACEUTICALS FRANCE**

miglustat

List I

Medicine for hospital prescription only

Orphan medicine

ATC code: A16AX06

Date of Marketing Authorisation: (centralized procedure): 24 February 2003

Date of extension of indication (centralized procedure): 26 January 2009

Reason for request:

Inclusion on the list of medicines approved for hospital use in the extension of indication: "ZAVESCA is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease".

*A Marketing Authorisation has been granted "under exceptional circumstances" for this medicinal product in this extension of indication. This means that, because the disease is rare, it is not possible to obtain complete information on the medicine. Every year, the EMEA will review any new information on this medicine and the SPC will be updated as necessary.*

Medical, Economic and Public Health Assessment Division

## 1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

miglustat

### 1.2. Indications

“ZAVESCA is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable”.

This indication has already been evaluated by the Committee, cf. opinion dated 12 November 2003.

**ZAVESCA is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease<sup>1</sup>”.**

### 1.3. Dosage in the new indication

“Therapy should be directed by physicians who are knowledgeable in the management of Gaucher disease or Niemann-Pick type C disease, as appropriate. ZAVESCA can be taken with or without food.

The recommended dose for the treatment of adult and adolescent patients with Niemann-Pick type C disease is 200 mg three times a day.

Dosing in patients under the age of 12 years should be adjusted on the basis of body surface area as illustrated below:

Body surface area (m <sup>2</sup> )	Recommended dose
> 1.25	200 mg three times a day
> 0.88 - 1.25	200 mg twice a day
> 0.73 - 0.88	100 mg three times a day
> 0.47 - 0.73	100 mg twice a day
≤ 0.47	100 mg once a day

Temporary dose reduction may be necessary in some patients because of diarrhoea. The benefit to the patient of treatment with ZAVESCA should be evaluated on a regular basis.

There is limited experience with the use of ZAVESCA in Niemann-Pick type C disease patients under the age of 4 years.

<sup>1</sup> Neumann-Pick type C disease is a lysosomal neurodegenerative disease characterized by accumulation of unesterified cholesterol and glycolipids (particularly cerebral glycosphingolipids) associated with intracellular cholesterol transport abnormalities caused by a genetic mutation.

The neurological manifestations determine the severity of the disease and can be used to differentiate between a number of forms:

- The early infantile form (22% of cases) which presents around the age of 12-18 months with delayed motor development associated with hypotonia followed by loss of motor skills. There is progression towards upper motor neurone lesions and a bedridden state and death occurs between the age of 3 and 6
- The late infantile form (29% of case): presents around the age of 2-5 with an ataxic gait. Death usually occurs around the age of 10
- The juvenile form (30% of cases): presents around the age of 6-12 with learning difficulties, epilepsy, cataplectic episodes or ophthalmoplegia. The course is marked by upper motor neurone lesions, motor regression culminating in a bedridden state, psychotic episodes. Death usually occurs in the 2nd decade of life
- The adult form (19% of cases): the symptoms resemble those associated with the juvenile form, sometimes accompanied by significant psychiatric disturbances

### Renal Impairment

Pharmacokinetic data indicate increased systemic exposure to miglustat in patients with renal impairment.

In patients with an adjusted creatinine clearance of 50–70 ml/min/1.73 m<sup>2</sup>, administration should commence at a dose of 200 mg twice daily (adjusted for body surface area in patients below the age of 12) in patients with Niemann-Pick type C disease.

In patients with an adjusted creatinine clearance of 30–50 ml/min/1.73 m<sup>2</sup>, administration should commence at a dose 100 mg twice daily (adjusted for body surface area in patients below the age of 12) in patients with Niemann-Pick type C disease.

Use in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m<sup>2</sup>) is not recommended.

### Hepatic Impairment

ZAVESCA has not been evaluated in patients with hepatic impairment.”

## 2. SIMILAR MEDICINAL PRODUCTS

### **2.1. ATC classification (2009)**

A	Alimentary tract and metabolism
A16	Other alimentary tract and metabolism products
A16A	Other alimentary tract and metabolism products
A16AX	Various alimentary tract and metabolism products
A16AX06	Miglustat

### **2.2. Medicines in the same therapeutic category**

There is no comparator medicine at present. ZAVESCA is the only medicinal product to be indicated in Niemann-Pick type C disease.

### **2.3. Medicines with a similar therapeutic aim**

Not applicable

The treatments used at present are symptomatic and palliative (cf. “Therapeutic use”).

## 3. ANALYSIS OF AVAILABLE DATA

The company submitted a dossier consisting of:

- a comparative, randomized, open-label clinical study with the objective of evaluating the efficacy and safety of miglustat (ZAVESCA), compared with no treatment, after 1 year of treatment in 29 patients (adults and adolescents). This trial also included 12 children, all treated with miglustat (exploratory analysis)
- a retrospective cohort documenting neurological symptoms before and after treatment with miglustat in 66 patients
- a retrospective cohort documenting the natural course of the neurological symptoms in 57 patients which will not be described because no patient was treated with miglustat
- retrospective data from individual case reports

### 3.1. Efficacy

#### 3.1.1. Results of the prospective clinical study OGT 918-007<sup>2</sup>

##### Methodology and objective:

Phase II, comparative, open-label clinical study, randomized in a ratio of 2:1, the main objective of which was to evaluate the efficacy of treatment with miglustat, with specific reference to the neurological manifestations (by measurement of saccadic eye movement speed), and its safety in patients with Niemann-Pick type C disease compared with no treatment after 12 months of treatment<sup>3</sup>.

It examined two distinct populations:

- adults and adolescents over 12 years of age within the scope of a comparative analysis (n=29, 20 patients in the miglustat group, 9 in the no treatment group)
- children aged between 4 and 12 within the scope of a descriptive analysis (n=12)

This study was the subject of a 12-month extension during which all the patients were treated with miglustat.

For compassionate reasons, because of the lack of treatment for this disease, children under 12 years of age could be included in the study if the investigator considered it safe and appropriate to do so. All the patients in this group were treated with miglustat for 24 months and there was therefore no control group.

##### Inclusion criteria:

- to be 12 years of age or older (for the study in adults and adolescents) or between 4 and 11 years of age (for the study in children)
- diagnosis of Niemann-Pick type C disease confirmed by a reduction in intracellular cholesterol esterification and positive filipin staining

##### Exclusion criteria:

- diarrhoea (more than 3 bowel movements/day for more than 7 days) without a specific cause in the 3 months prior to inclusion or a history of gastro-intestinal complaints
- any other serious disease (hepatitis, HIV infection)
- estimated creatinine clearance < 70 ml/min/1.73 m<sup>2</sup>
- administration of treatments capable of interfering with absorption or gastro-intestinal motility
- women of childbearing age, without adequate contraception

##### Administration regimen:

The adult and adolescent patients were randomized to receive miglustat at a dosage of 200 mg 3 times daily. Both patient groups (treated with miglustat or untreated) received standard care (notably using physiotherapy and occupational therapy)<sup>4</sup>.

The children were treated with miglustat at an initial dose of 200 mg 3 times daily adjusted for body surface area, in conformity with the SPC.

The dose could be reduced in the event of gastro-intestinal intolerance, frequent with miglustat.

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<sup>2</sup> Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE.. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol* 2007;6(9):765-72

<sup>3</sup> two centres were involved: one in the United States and one in the United Kingdom

<sup>4</sup> the concomitant treatments were: paracetamol in 5/28 patients, benzodiazepines in 4/28 patients, vitamins in 3/28 patients, ibuprofen in 3/28 patients, antidepressants in 3/28 patients

### Primary efficacy endpoint:

Measurement of horizontal saccadic eye movements after 1 year of treatment, evaluated using the slope for horizontal saccadic eye movement (HSEM- $\alpha$ ). The latter is obtained from the graph of saccadic eye movement speed versus amplitude (in degrees) which enables the saccadic eye movements of a patient to be characterized at a given time<sup>5,6</sup>.

When the amplitude and speed of saccadic eye movements decrease as is seen in Niemann-Pick C disease, there is an increase in the angle  $\alpha$  of the regression slope estimated on the basis of the graph. Conversely, the slope decreases when there is an improvement in the saccadic eye movements.

*Note: Abnormal saccadic eye movements are found as an almost constant feature in patients with Niemann-Pick type C disease and have been shown to correlate with disease progression<sup>7</sup>. The deterioration in vertical movements is almost always present, whereas the deterioration in horizontal movements appears gradually as the disease progresses, culminating in complete paralysis. The choice of this clinical manifestation as an endpoint is questionable because it is not a clinically significant neurological sign (expert opinion).*

This endpoint was the subject of an exploratory analysis in the subgroup of patients who had not received benzodiazepines, which are liable to interfere with HSEM- $\alpha$  assessment<sup>8</sup>. The results of this analysis will not be described.

### Main secondary endpoints :

- HSEM- $\beta$ <sup>9</sup>
- Swallowing assessment<sup>10</sup>
- assessment of physical performance using an ambulation test (Hauser Ambulation index<sup>11</sup> validated in other neuro-degenerative diseases<sup>12</sup>).
- assessment of cognitive function (MMSE)<sup>13</sup>
- quality of life<sup>14</sup>

Other secondary endpoints: liver and spleen volume, complete neurological assessment with measurement of nerve conduction speed, tremor assessment.

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<sup>5</sup> Inchingolo P, Spanio M. On the identification and analysis of saccadic eye movements-a quantitative study of the processing procedures. IEEE Trans Biomed Eng 1985;32(9):683-95

<sup>6</sup> Solomon D, Winkelman AC, Zee DS, Gray L, Büttner-Ennever J. Niemann-Pick type C disease in two affected sisters: ocular motor recordings and brain-stem neuropathology. Ann N Y Acad Sci 2005 ;1039:436-45

<sup>7</sup> Lengyel D, Weissert M, Schmid L, Gottlob I. [Eye movement abnormalities as a sign for the diagnosis in Niemann-Pick disease type C]. Klin Monatsbl Augenheilkd 1999; 214(1):50-2

<sup>8</sup> Kroboth PD, Folan MM, Bauer KS, Tullock W, Wright CE, Sweeney JA.. Do alprazolam-induced changes in saccadic eye movement and psychomotor function follow the same time course? J Clin Pharmacol. 1998 Apr;38(4):337-46

<sup>9</sup> measurement of saccadic eye movements corresponding to the intersection of the regression slope with the maximum duration axis (amplitude zero). A reduction in the value is identified when there is an improvement in the HSEM speed

<sup>10</sup> swallowing difficulties, a major complication in the course of the disease, is associated with the risk of poor nutrition and pulmonary complications which can be fatal if something is swallowed the wrong way, hence the need to resort to gastrostomy in the terminal stage of the disease

<sup>11</sup> each patient had to ambulate 8 metres. Mobility and the degree of support were assessed on the basis of this index with a score of between 0 (asymptomatic, completely active) and 9 (in a wheelchair, loss of independence)

<sup>12</sup> Hauser SL, Dawson DM, Leirich JR, Beal MF, Kevy SV, Propper RD, Mills JA, Weiner HL.. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. N Engl J Med 1983; 308(4):173-80

<sup>13</sup> the study population of adults and adolescents was evaluated using the Folstein's Mini Mental Status Exam (MMSE). The parameters assessed are orientation to time and place, attention, immediate and recall memory, calculation, language and constructional ability. The maximum overall score is 30 points, with a score below 24 indicating the existence of cognitive disturbances

<sup>14</sup> evaluated with the aid of the generic SF-36 questionnaire (short version) with physical and mental components. The 8 areas assessed are: physical functioning, role physical, bodily pain, social functioning, mental health, role emotional, vitality, general health. Two composite scores are then calculated: the physical composite score and the mental composite score.

Post hoc analyses were performed, evaluating the response to treatment in terms of improvement, stabilisation or worsening of certain endpoints compared with baseline. The methodological level of these analyses does not enable any conclusions to be drawn. The results of these analyses are not described.

Patient characteristics on inclusion (Table 1):

The average age of the patients was  $25.4 \pm 9.8$  in the miglustat group,  $22.9 \pm 7.5$  in the untreated group. The children included in the study were aged  $7.2 \pm 2.5$  on average.

It should be noted that the number of patients in the control group was small, with younger patients and patients at a less advanced disease stage. Neurological involvement was more frequent in the group of adults/adolescents treated with miglustat than in the untreated group (particularly vertical gaze palsy and ataxia which affected all the patients treated with miglustat, whatever their age).

Organ enlargement was more frequent in the children than in the adults and adolescents.

Table 1: Clinical characteristics of the patients on inclusion

Signs present	Adults/adolescents		Children
	Miglustat group (N=20)	Control group (N=9)	Miglustat (N=12)
<b>Neurological signs</b>	n	n	n
Vertical gaze palsy	20	7	12
Ataxia	20	5	1
Cognitive deficit	18	7	8
Language articulation difficulties	18	4	7
Dystonia	14	4	5
Swallowing difficulties	12	6	4
Upper motor neurone disturbances	10	3	5
Epilepsy	1	1	0
Cataplexia	1	0	4
<b>Organ enlargement</b>			
Spleen enlargement	7	5	10
Liver enlargement	6	4	7

The results are derived from an analysis of all the patients who were randomized and received at least one dose of treatment, with baseline data and at least one measurement during treatment.

3.1.1.1. Results of the comparative study conducted in the adolescent and adult population

Primary endpoint:

Initially, the HSEM- $\alpha$  value was 3.038 ms/deg in the miglustat group and 2.432 ms/deg in the untreated group.

Table 2 :

HSEM- $\alpha$ criterion (ms/deg)	Average change adjusted for baseline value		Estimated difference 95% CI	p
	Miglustat group	Untreated group		
At 1 year (n=17)	-0.329	-0.055	- 0.274 [-0.959; +0.411]	NS
Compared with last available value (n =18)	-0.376	-0.050	- 0.326 [-1.000; +0.348]	NS

No difference was observed between the miglustat group and the untreated group in terms of the measurement of horizontal saccadic eye movements (HSEM- $\alpha$ ) after 1 year of treatment.

#### Main secondary endpoints:

##### - HSEM-β

At 12 months, an increase in this value, indicating a deterioration, was identified in both groups, but the difference observed between the treatments was not significant.

##### - Swallowing assessment

A significant improvement was observed in the miglustat group compared with the untreated group for the biscuit test ( $p = 0.044$ ) and for the purée test at 6 months ( $p = 0.043$ ). The other tests did not show any significant difference.

##### - Assessment of physical performance using an ambulation test (Hauser Ambulation index)

On inclusion, the ambulation index was higher in the miglustat group (2.4) than in the untreated group (0.9).

After 1 year of treatment, the value for this index had increased by +0.2 in the miglustat group and by +0.7 in the untreated group (NS).

##### - Assessment of cognitive function (MMSE)

After 1 year, the MMSE score had changed from 22.8 points ( $\pm 5.2$ , score on inclusion) to 24.0 ( $\pm 5.6$ ) in the miglustat group. In the untreated group, this score changed from 23.4 ( $\pm 4.9$ ) to 23.1 ( $\pm 5.7$ ).

##### - Quality of life

After 12 months of treatment, an improvement was noted for 4 of the 8 areas covered by the SF-36 questionnaire (bodily pain, general health, social functioning, mental health) and in the composite physical score in the miglustat group compared with the untreated group.

A deterioration in 3 areas (vitality, physical functioning, role emotional) was observed in the miglustat group with no statistical significance between the groups.

#### Results after 24 months:

25/29 patients, all treated, participated in the 12-month extension phase. Two groups were compared: the group of patients initially treated with miglustat (17 patients treated with miglustat over 24 months), the group of patients from the untreated group (8 patients treated with miglustat over 12 months). The results are available for 19/25 patients (15 treated for 24 months with miglustat, 4 treated for 12 months).

No statistically significant difference was observed between these 2 groups in terms of the primary endpoint or the secondary HSEM-β endpoint.

Around ten patients experienced stabilisation or an improvement in their swallowing in the group treated for 24 months with miglustat, 2 in the other group.

A statistically significant difference was observed between the 2 groups for the ambulation test<sup>15</sup> ( $-1.377$  CI95%  $[-2.720 ; -0.034]$ ,  $p=0.045$ ).

Cognitive function was not assessed in a sufficient number of patients (9 in total).

#### 3.1.1.2. Results of the trial conducted in children under 12 years of age

##### Primary endpoint:

The HSEM-α endpoint value changed from +2.201 ( $\pm 1.217$ ) ms/deg on inclusion to -0.465 ( $\pm 0.127$ ) ms/deg.

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<sup>15</sup> difference observed compared with the last available value

### Secondary endpoints:

#### - HSEM- $\beta$

The value for this endpoint increased by 4.533 ms after 12 months of treatment compared with baseline, which indicates a deterioration. Furthermore, this value is higher than that observed in the adults and adolescents in absolute terms.

#### - Swallowing assessment

Eight of the 12 children did not have any difficulties at baseline, which made it difficult to assess the change in swallowing difficulties after 12 months. An improvement was noted in 1 child and a deterioration in 3 children.

#### - Assessment of physical performance using an ambulation test (Hauser Ambulation index)

An increase in the ambulation index (+0.4), corresponding to a deterioration in ambulation, was observed after 12 months. This increase was similar to that observed in adults and adolescents.

#### - Quality of life

The questionnaire was not analyzed because it was completed by a small number of children.

### Results after 24 months

Ten patients were assessed. The average HSEM- $\alpha$  value decreased by -0.075 ( $\pm$  1.235) ms/deg. The HSEM- $\beta$  value increased by 4.514 ms and the ambulation score by +0.6.

### **3.1.2. Results for the epidemiological cohorts**

Two epidemiological surveys were submitted by the company.

The first survey collected retrospective data from patients with Niemann-Pick type C disease treated with miglustat off-label. The objective of this study was to document the effects of miglustat in daily practice.

The aim of the second epidemiological survey was to document the natural history of the disease in order to gain a better understanding of the neurological progression of the disease in particular. This study will not be described in the present document since it does not enable the efficacy and safety of miglustat to be documented, because no patients were treated with miglustat in this cohort.

The endpoint for neurological involvement was the disability scale specific to the disease developed by a Spanish team<sup>16</sup>. This scale examines the 4 main items affected by the disease: ambulation, manipulation, language function/articulation and swallowing. The severity to which each item is affected is scored separately, and a composite score (average of each individual score) is then calculated. Iturriaga's scale was modified for cohort analysis, with each item being assigned a score ranging between 0 (no disability) and 1 (maximum disability) instead of between 1 and 4 or 5, in order to avoid giving too much importance to scores of up to 5.

The analysis focused on the rate of disease progression. The individual score for each item was analyzed in a qualitative manner: improvement, stabilisation, deterioration, modified global Iturriaga score.

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<sup>16</sup> Iturriaga C, Pineda M, Fernández-Valero EM, Vanier MT, Coll MJ. Niemann-Pick C disease in Spain: clinical spectrum and development of a disability scale. J Neurol Sci 2006;249:1-6



Table 3: Modified disability scale

ITEMS	Modified score
<b>Ambulation</b>	
. Normal	0
. Autonomous ataxic gait	0.25
. Outdoor assisted ambulation	0.50
. Indoor assisted ambulation	0.75
. Wheelchair-bound	1
<b>Manipulation</b>	
. Normal	0
. Slight dysmetria/dystonia (allows autonomous manipulation)	0.33
. Mild dysmetria/dystonia (requires help for several tasks; able to feed himself)	0.67
. Severe dysmetria/dystonia (requires assistance in all activities)	1
<b>Language function/articulation</b>	
. Normal	0
. Mild dysarthria (understandable)	0.25
. Severe dysarthria (only comprehensible to some members of the family)	0.50
. Non-verbal communication	0.75
. Absence of communication	1
<b>Swallowing</b>	
. Normal	0
. Occasional dysphagia	0.33
. Daily dysphagia	0.67
. Naso-gastric tube or gastric button feeding	1

## Results

Sixty-six patients (36 children and 30 adults/adolescents) were included. The average age at diagnosis was  $9.7 \pm 7.6$  and on instigation of treatment  $12.8 \pm 9.5$ . The average duration of treatment with miglustat was 1.5 years.

The average miglustat dose, documented for 61 patients, was 350.9 mg/day.

Stabilisation of the following parameters was observed in more than 60% of patients treated with miglustat and a deterioration in 20-25% of the patients: ambulation, manipulation, language function/articulation, swallowing.

A qualitative analysis was performed based on the number of functions which were stable or improved after treatment with miglustat.

Improvement or stabilisation of 3-4 functions was observed in 49/66 patients, 17/26 children under 6 years of age, 20/22 patients over 12 years of age.

The average disability score changed:

- from 0.18 at diagnosis to 0.43 on instigation of treatment and to 0.48 at the last visit or on discontinuation of treatment for "ambulation"
- from 0.27 at diagnosis to 0.48 on instigation of treatment and to 0.52 at the last visit or on discontinuation of treatment for "manipulation"
- from 0.16 at diagnosis to 0.31 on instigation of treatment and to 0.37 at the last visit or on discontinuation of treatment for "language function/articulation"
- from 0.12 at diagnosis to 0.36 on instigation of treatment and to 0.37 at the last visit or on discontinuation of treatment for "swallowing"

The composite score (average of scores for each function) was calculated for each patient. The average for this score was 0.20 at diagnosis (n = 65), 0.41 on introduction of miglustat (n = 66) and 0.45 at the last visit or on discontinuation of treatment (n = 65).

In addition, a regression analysis performed on a number of variables shows that the age at diagnosis is a predictive factor for response to treatment.

The investigators considered that 37% of the patients improved and 40% remained stable under treatment.

The assessment of the overall benefit of treatment with miglustat to the patient was considered good for 41% or quite good for 33% of the patients.

### **3.1.3 Individual case reports** <sup>17, 18, 19, 20</sup>

The Marketing Authorisation dossier also includes 14 retrospectively documented individual case reports relating to patients treated with miglustat. Progress under miglustat was rated as positive for 10 patients, negative for one and undocumented in the 4 remaining cases.

## **3.2. Tolerance data**

### **3.2.1 from the pivotal Marketing Authorisation study OGT 918-007**

All the patients had at least one adverse event.

Nervous system involvement affected 9/12 children, all the adolescents and adults and 8/9 patients from the untreated group. These effects were mainly abnormal gait in the children and patients in the untreated group, tremor in the adolescents and adults, spastic gait in the adults.

Weight loss was observed in 3/12 children, 8/15 adults and all the adolescents. In most cases, the weight loss was less than 20%. However, 1 patient in the adult/adolescent group lost at least 20% of his weight. None of the patients in the untreated group experienced weight loss.

The analysis of the percentile changes (adjusted for gender and age) in the height of patients under 20 years of age showed a reduction in growth after 6 months and 1 year of treatment. After this, the average height remained stable in the same percentile.

Gastro-intestinal effects, mainly diarrhoea, affected 8/12 children, all the adolescents and the adults from the treated group, and 6/9 patients from the untreated group.

The miglustat dosage was reduced because of adverse effects in 3 patients from the adult/adolescent group (1 case of diarrhoea, 1 case of tremor, 1 case of diarrhoea and tremor) and in 2 children (1 case of diarrhoea, 1 case of tremor).

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<sup>17</sup> Lachmann RH, te Vruchte D, Lloyd-Evans E, Reinkensmeier G, Sillence DJ, Fernandez-Guillen L, Dwek RA, Butters TD, Cox TM, Platt FM Treatment with miglustat reverses the lipid-trafficking defect in Niemann-Pick disease type C. *Neurobiol Dis.* 2004 16(3):654-8

<sup>18</sup> Chien YH, Lee NC, Tsai LK, Lee NC, Huang AC, Peng SF, Chen SJ, Hwu WL. Treatment of Niemann-Pick disease type C in two children with miglustat: initial responses and maintenance of effects over 1 year. *J Inherit Metab Dis* 2007;30(5):826

<sup>19</sup> Paciorkowski AR, Westwell M, Ounpuu S, Bell K, Kagan J, Mazzarella C, Greenstein RM. Motion analysis of a child with Niemann-Pick disease type C treated with miglustat. *Mov Disord* 2008;23(1):124-8

<sup>20</sup> Santos ML, Raskin S, Telles DS, Löhr Junior A, Liberalesso PBN, Vieira SC, Cordeiro ML. Treatment of a child diagnosed with Niemann-Pick disease type C with miglustat: A case report in Brazil. *J Inherit Metab Dis* 2008; October 21

### **3.2.2 from the 8th PSUR**

The analysis of the data from the last international PSUR for ZAVESCA (covering the period from October 2007 – October 2008) is consistent with the information on risk as it appears in the current Marketing Authorisation. The most common adverse events are diarrhoea, weight loss, tremor and neurological symptoms.

### **3.3. Conclusion**

The company supplied notably the results of a comparative clinical study and of a retrospective epidemiological survey.

The main objective of the Phase II, comparative, randomized, open-label clinical study was to compare the efficacy and safety of miglustat after 12 months in patients with Niemann-Pick type C disease.

It included two distinct populations:

- 29 adults and adolescents over 12 years of age within the scope of a comparative analysis (20 patients in the miglustat group, 9 in the no treatment group)
- 12 children aged between 4 and 12 within the scope of an exploratory analysis

After 1 year of treatment, no difference was observed between the miglustat and the untreated groups in terms of the main efficacy endpoint (reduction in saccadic eye movements).

The analysis of the secondary endpoints did not show a statistically significant difference between the groups, except for swallowing; a significant improvement in favour of miglustat was observed for the "biscuit" test.

Two groups were compared during the 12-month extension phase: the group of patients initially treated with miglustat (17 patients treated with miglustat for 24 months) and the group of patients from the untreated group (8 patients treated with miglustat for 12 months). The results are available for 19/25 patients. After 2 years, no difference was observed between these 2 groups on the basis of the criteria assessed except for swallowing which improved or stabilized in ten patients in the group treated with miglustat for 24 months and in 2 patients in the group treated for 12 months.

The study in children (because of its methodology and the small number of patients included) does not provide a basis for a quantitative assessment of the effect observed and for drawing a formal conclusion with regard to the benefit provided to the patient.

In a retrospective epidemiological survey which had the objective of describing the changes in neurological manifestations in 66 patients with Niemann-Pick type C disease, stabilisation of the following parameters was observed in more than 60% of the patients treated with miglustat and worsening in 20-25% of the patients: ambulation, manipulation, language function/articulation, swallowing. These results must be interpreted with caution in view of the methodology of the survey.

The data available do not permit a formal conclusion to be drawn regarding the efficacy of miglustat in Niemann-Pick type C disease. However, the results of the studies suggest that, in patients treated with miglustat, the course of the disease is different from that expected and that this modification of the natural history of the disease is more notable in the less severe patients, in the moderate forms (expert opinion), in which cases the disease is less progressive.

Miglustat is thus, at present, the only treatment available for the progressive neurological manifestations, but its benefit is modest, only slowing down progression for certain parameters (swallowing, ambulatory index).

The most common adverse events are diarrhoea, weight loss and tremor.

The safety profile of miglustat in Niemann-Pick type C disease is the same overall as that observed in type 1 Gaucher disease.

The SPC specifies that “the benefit of treatment with ZAVESCA for neurological manifestations in patients with Niemann-Pick type C disease should be evaluated on a regular basis, e.g. every 6 months; continuation of therapy should be re-appraised after at least 1 year of treatment with ZAVESCA. Reduced growth has been reported in some paediatric patients with Niemann-Pick type C disease in the early phase of treatment with miglustat where the initial reduced weight gain may be accompanied or followed by reduced height gain. Growth should be monitored in paediatric and adolescent patients during treatment with ZAVESCA; the benefit/risk balance should be re-assessed on an individual basis for continuation of therapy”.

A register specifically dedicated to following up patients with Niemann-Pick type C disease is being set up by the company at the request of the EMEA.

The aim of this register will be to describe the natural history of the disease and its progression under the real life conditions of patients, to describe the treatment experiences of the patients, to ensure good compliance with the recommendations of the SPC and to collect specific safety information relating to the patients treated with ZAVESCA.

## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Niemann-Pick type C disease is a rare, serious genetic disease with neuro-gastrointestinal involvement caused by lysosomal accumulation of non-esterified cholesterol and certain glycosphingolipids. It is characterized by various debilitating and progressive neurological symptoms.

Extensive clinical heterogeneity exists with an age of onset varying between the perinatal period and advanced adult age (over 50). The age of onset and the course of the neurological symptoms determine the severity of the disease which is associated with an inevitably worsening course.

ZAVESCA comes within the scope of symptomatic treatment.

Taking into account the level of proof provided by the data available, the improvement in the neurological symptoms characteristic of the disease and the benefit provided to the patients are difficult to assess. It seems that no benefit can be expected in patients with a neurological form with an early infantile onset or which is already at a very advanced and severe stage, but ZAVESCA may be offered to patients with less progressive, i.e. moderate forms.

The efficacy/adverse effects ratio for ZAVESCA is therefore modest.

There are no pharmacological alternatives to this proprietary medicinal product. The treatments used at present are symptomatic and palliative.

#### Public health benefit:

Niemann-Pick type C disease is a serious genetic disease associated with a high risk of morbidity and mortality but constitutes a low public health burden because of its rarity (orphan disease).

Because improving the management of orphan diseases is one of the identified priorities (GTNDO\*, Rare Diseases Plan), the treatment of this condition is a public health need.

In view of the data available, the anticipated impact of the proprietary medicinal product ZAVESCA in terms of morbidity and mortality and quality of life is difficult to quantify.

The response to the identified public health need provided by the proprietary medicinal product ZAVESCA is not guaranteed.

As a consequence, in the current state of knowledge, it is not expected that this proprietary medicinal product will benefit public health.

\*Groupe Technique National de Définition des Objectifs (DGS) = National Technical Group for Defining Objectives (General Directorate of Health)

The actual benefit of ZAVESCA is moderate.

#### **4.2. Improvement in actual benefit (IAB)**

ZAVESCA provides a minor improvement in actual benefit (IAB IV) in the treatment of the progressive neurological manifestations of the moderate forms of Niemann-Pick type C disease.

#### **4.3. Therapeutic use**

No specific treatment exists. Because of the intracellular abnormalities of cholesterol metabolism, cholesterol-lowering agents have been tried but without any effect on the neurological symptoms.

The medicinal products used for the symptomatic or palliative treatment of the various neurological disturbances are: anticholinergic agents and botulinum toxin for the dystonias and tremor, anti-epileptic agents, tricyclic antidepressants and stimulants for the cataplexia, analgesic agents. These treatments have not shown that they modify the course of the disease, particularly the progression of neurological symptoms.

The non-pharmacological management of Niemann-Pick type C disease is essential in order to maintain functional capacities and an acceptable quality of life for the patient. It includes dietetic/nutritional care, speech therapy, physiotherapy, psychological support or psychiatric management.

Feeding by tube or gastrostomy is necessary in the advanced stage of the disease because of the risk of swallowing something the wrong way, secondary respiratory infections and poor nutrition caused by the swallowing difficulties.

ZAVESCA is the first medicinal product indicated for the treatment of progressive neurological manifestations in patients with Niemann-Pick type C disease.

Taking into account its mode of action<sup>21</sup> and the pathophysiology of the disease, ZAVESCA has a modest effect on slowing the progression of moderate forms of the disease.

This medicinal product is indicated only in cases of onset of neurological signs, the time to onset of which varies between patients.

ZAVESCA must be prescribed in one of the reference centres for hereditary diseases of metabolism or lysosomal diseases. The efficacy of ZAVESCA must be evaluated regularly as specified in the SPC, and in the absence of efficacy or if the neurological deterioration continues the treatment must be withdrawn following the advice of the CETNP/ Comité d'Evaluation du Traitement des maladies de Niemann-Pick (committee for the evaluation of treatment of Niemann-Pick diseases).

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<sup>21</sup> miglustat is an inhibitor of glucosylceramide synthetase (enzyme involved in the 1st stage of sphingolipid synthesis) which crosses the blood-brain barrier

#### **4.4. Target population**

The prevalence at birth of patients with Niemann-Pick type C disease is around 1 case per 150,000 births in Western Europe. The analysis of the French cohort showed a prevalence at birth of 1 case per 125,000 births over the last 20 years including fetuses with Niemann-Pick type C disease.

On the basis of the prevalence at birth which is 1/125,000 births in France and the total number of births being 801,000 children born in 2008<sup>22</sup>, the annual estimate of new cases is 6 children.

Because the adult forms of the disease are underdiagnosed owing to the fact that their symptoms are not very specific, it is difficult at present to assess the changes in the target population over time in a precise manner.

Among the forty or so patients with Niemann-Pick type C disease living and known in France, 12 patients are currently benefiting from treatment with ZAVESCA within the scope of a dispensatory protocol set up by the health authorities in 2007.

The other patients are either unsuitable candidates for treatment at present or, in the absence of a specific treatment available before 2007, have reached a neurological stage which is too advanced (patients with dementia, bedridden on with gastrostomy) to be able to benefit from treatment with ZAVESCA.

#### **4.5. Transparency committee recommendations**

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the new indication and at the posology in the Marketing Authorisation.

The Transparency Committee wishes to be supplied with:

- the results of the data from the register set up by the company as part of the monitoring programme requested by the EMEA and specifically dedicated to following up patients with Niemann-Pick type C disease
- and any data submitted to the EMEA as part of the annual review of the Marketing Authorisation granted under exceptional circumstances

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<sup>22</sup> INSEE. Bilan démographique 2008 (demographic assessment 2008). Insee.fr.