HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

Opinion

6 June 2007

DIACOMIT 250 mg, capsule-container (PP)
B/ 60 (CIP: 378 322-1)
DIACOMIT 500 mg, capsule-container (PP)
B/ 60 (CIP: 378 325-0)
DIACOMIT 250 mg, powder for oral suspension in sachet
B/ 60 (CIP: 378 329-6)
DIACOMIT 500 mg, powder for oral suspension in sachet
B/ 60 (CIP: 378 332-7)

Applicant: BIOCODEX

Stiripentol
ATC Code: N03AX17

List I
Medicinal product for initial hospital prescription for six-month periods, reserved for use by paediatricians and neurologists. Unrestricted renewal.
Medicinal product requiring specific monitoring during treatment
Orphan medicinal product

Date of Conditional Marketing Authorization (EMEA): January 4, 2007

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Stiripentol

1.2. Background
Stiripentol is an allyl alcohol, not structurally related to other antiepileptic drugs.

1.3. Indication
DIACOMIT is indicated for use in conjunction with clobazam and sodium valproate as adjunctive therapy of generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and sodium valproate.

1.4. Dosage (see SmPC)
DIACOMIT should only be administered under the supervision of a paediatrician or a paediatric neurologist experienced in the diagnosis and treatment of epilepsy in infants and children. The dose is calculated on a mg/kg body weight basis. The daily dosage may be administered in two or three divided doses.

The initiation of adjunctive therapy with clobazam and sodium valproate should be made over three days using upwards dose-escalation to reach the recommended dose of 50 mg/kg/day. This recommended dose is based on the available clinical study findings and was the only dose evaluated during pivotal studies of DIACOMIT.

There are no clinical data supporting the clinical safety of DIACOMIT administered at daily doses greater than 50 mg/kg/day.

There are no clinical data supporting the use of DIACOMIT as monotherapy in the treatment of Dravet's syndrome.

<u>Dose adjustments of other antiepileptics used in combination with DIACOMIT</u>
Despite the absence of exhaustive pharmacological data about potential drug interactions, the following recommendations regarding dosage adjustment of other antiepileptics combined with DIACOMIT are provided on the basis of clinical experience:

- Clobazam

  In the pivotal studies, the dose of clobazam on initiation of DIACOMIT was 0.5 mg/kg/day usually administered in divided doses, twice daily. This daily dose was reduced by 25% every week if side effects or clinical signs of clobazam overdosage (drowsiness, hypotonia, and irritability in young children) were observed. Co-administration of DIACOMIT in children with Dravet's syndrome increased plasma clobazam concentrations by approximately two or three times and norclobazam levels by approximately five times.
- Sodium valproate

  The potential for drug interactions between DIACOMIT and sodium valproate is considered modest. Therefore no change in valproate dosage should be needed when DIACOMIT is added, except for reasons of clinical safety. In the pivotal studies, the daily dose of valproate was reduced by approximately 30% per week in the case of gastrointestinal adverse reactions such as anorexia or weight loss.

Effect of formulation
Bioequivalence between the capsules and oral suspension formulations has not been established. Clinical monitoring is recommended if changing stiripentol formulations.

Children aged less than three years
Pivotal studies were conducted in children aged three years or more with SMEI. The clinical decision for use of DIACOMIT in children aged less than 3 years with SMEI must be made on an individual patient basis; by taking into account the potential benefits and clinical risks. In these younger children, adjunctive treatment by DIACOMIT should only be started after clinical confirmation of the diagnosis of SMEI. Data are limited about the use of DIACOMIT in children under 12 months of age.

1.5 Pharmacodynamic properties (cf. SmPC)
DIACOMIT has been found to increase cerebral concentrations of gamma-aminobutyric acid (GABA). This phenomenon seems to be due to the inhibition of synaptosomal uptake of GABA and/or inhibition of GABA-transaminase. DIACOMIT has also been shown to enhance GABA-A receptor-mediated transmission in the immature rat hippocampus and increase the mean open-duration (but not the frequency) of chloride channels of this same receptor by a barbiturate-like mechanism.

Because of pharmacokinetic interactions, stiripentol potentiates the effect of other anticonvulsants such as carbamazepine, sodium valproate, phenytoin, phenobarbital and many benzodiazepines. The second effect of stiripentol is mainly based on metabolic inhibition of several CYP450 iso-enzymes, in particular 3A4 and 2C19, involved in hepatic metabolism of other antiepileptics.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification
ATC 2007:
- N: Nervous system
- N03: Antiepileptics
- N03A: Antiepileptics
- N03AX: Other antiepileptics
- N03AX17: Stiripentol

2.2. Medicines in the same therapeutic category
None

2.3. Medicines with a similar therapeutic aim
No other proprietary medicine is specifically indicated in the treatment of generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI).

Sodium valproate (DEPAKINE) and clobazam (URBANYL) are traditionally used in SMEI. These proprietary medicines have a Marketing Authorisation (MA) in the treatment of partial or generalised seizures in adults and children.

DEPAKINE is also indicated in the child in the “prophylaxis of breakthrough seizures after one or more febrile convulsion, presenting criteria of complicated febrile convulsions, in the absence of efficacy of intermittent prophylaxis by benzodiazepines”.

Antiepileptics indicated in adjunctive therapy of generalised seizures, including tonic-clonic seizures:

- Valproic acid DEPAKINE 200 mg and 500 mg, enteric-coated tablets, DEPAKINE 57.64 mg/ml, syrup, DEPAKINE 200 mg/ml, oral solution, DEPAKINE CHRONO 500 mg, SR tablet and DEPAKINE 400 mg/4 ml, solution for injection (for infants, children and adults)
- Clonazepam RIVOTRIL 2 mg cross-scored tablets, RIVOTRIL oral solution 2.5 mg/ml (for infants, children and adults);
- Clobazam URBANYL 10 mg scored tablet and URBANYL 20 mg tablets (for infants, children and adults)
- Topiramate EPITOMAX 15 mg and 25 mg capsules, EPITOMAX 25 mg, 50 mg, 100 mg and 200 mg tablets (for children > 2 years and adults)

According to certain publications[1,2] and expert opinions, most other antiepileptic medicinal products such as carbamazepine, phenobarbital, phenytoin, vigabatrin, lamotrigine are ineffective and may increase the incidence of seizures and worsen the outcome of patients with SMEI.

3. ANALYSIS OF AVAILABLE DATA

The dossier comprises:

- Two comparative phase III studies, sodium valproate and clobazam combined with stiripentol or placebo, in severe myoclonic epilepsy in infancy (SMEI): STICLO France and STICLO Italy, which led to the granting of a conditional European MA.
- Analysis of the periodic safety update report within the scope of the cohort TUA (250 patients) and Patient-Named TUA.

3.1. Efficacy

3.1.1 STICLO Study France[3]

This randomised, double-blind, placebo-controlled study evaluated the efficacy and safety of stiripentol combined with clobazam and valproate, for 2 months, in 42 patients with severe myoclonic epilepsy in infancy. The patients were aged from 3 to 18 years, with SMEI that began before the age of 1 year and comprises at least 4 generalised clonic or tonic-clonic seizures per month.

After an initial treatment phase with valproate[4] /clobazam[5] for 1 month, the patients received for 2 months:

- stiripentol group (n = 22): sodium valproate (30 mg/kg/d) /clobazam (0.5 mg/kg/d, maximum dosage 20 mg/d) and stiripentol, 50 mg/kg/d in 2 or 3 doses per day (500 mg and 250 mg capsules).
- placebo group (n = 20): sodium valproate (30 mg/kg/d) /clobazam (0.5 mg/kg/d, maximum dosage 20 mg/d) and placebo in 2 or 3 doses per day (500 mg and 250 mg placebo capsules).

Patients were also given progabide or diazepam (intrarectally) when necessary.

1 DRAVET C. et al, Severe myoclonic epilepsy in infancy: Dravet Syndrome - Adv Neurol., 2005; 95: 71-102
2 SANKAR R. et al, Treatment of myoclonic epilepsies in infancy and early childhood - Adv. Neurol., 2005, 95: 289-298
3 Carried out between October 1996 and August 1998, CHIRON C. et al, Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome dedicated trial – The Lancet, 2000, November, 356 (9242): 1638-1642 and study report.
4 Amendment to the protocol (after the 20th enrolled patient): in the 1st version of the protocol, sodium valproate had to be given at 20 mg/kg/day before entry in the trial and reduced to 15 mg/kg/day (maximum 1,000 mg/day) at the start of the baseline period. As the relatively rapid reduction in dosages caused seizures in certain patients, the dosage of sodium valproate was reduced more slowly: during the baseline period, if the patients received a dose of sodium valproate greater than 30 mg/kg/day, a reduction to 30 mg/kg/day was tested. If this failed, the patient was left at the previous dose.
5 Maximum: 20 mg/day.

Primary endpoint:

- Number of responder patients (success) in whom the number of clonic or tonic-clonic seizures fell by at least 50% during the second month compared to the number of seizures during the baseline period.

Main secondary efficacy endpoints:

- Number of patients in whom the number of clonic or tonic-clonic seizures fell by at least 50% during the last month of the period of comparison (calculated for 30 days), compared to the number of seizures during the baseline phase (calculated for 30 days).
- Number of seizures during the comparison period (first and second month taken separately) calculated as a ratio of the number of seizures at baseline.

Assay of medicinal products: the plasma concentration of antiepileptic medicinal products was measured 1 week before final enrolment and 1 week before the end of the comparison period, i.e. after 7 weeks of treatment.

Results:

The age of enrolled patients was 9.4 ± 4.0 years (range 3.0 - 16.7) in the stiripentol group and 9.3 ± 4.9 years (range 3.2 - 20.7) in the placebo group. The mean number of tonic-clonic seizures during the initial phase (1 month) was 17.9 ± 17.3 (range 3.9-72.9) in the stiripentol group and 18.5 ± 17.0 (range 4.1-76.2) in the placebo group.

At baseline, resort to diazepam was necessary in 4/22 patients in the stiripentol group and 7/20 patients in the placebo group.

Primary endpoint: The number of responders was significantly higher in the stiripentol group (15/21 patients) than in the placebo group (1/20 patients) ($p<0.0001$)

Secondary endpoints:

Table 1: Change in the number of tonic-clonic seizures between the baseline phase and the end of the 2nd month

	Stiripentol (n = 20) *	Placebo (n = 16) *	Chi 2
No seizure	9	0	p< 0.01
Reduction >50% < 100%	6	1	
Reduction <50%	3	5	
Increase <50%	2	8	
Increase >50%	0	2	

*calculated on patients who completed the study. Patients who stopped treatment were not taken into account: 1 in the stiripentol group; 4 in the placebo group.

Nine patients in the stiripentol group had no tonic-clonic seizures during the two months of treatment versus no patient in the placebo group (p= 0.0013).

Table 2: Number of tonic-clonic seizures and change compared with baseline

	Stiripentol	Placebo	p (Mann and Whitney)
Initial phase (calculated for 30 days)	N =21	N =20	
Number of tonic-clonic seizures ± SD	17.9 ± 17.3	18.5 ± 17.0	NS
First month			
Number of tonic-clonic seizures ± SD	2.72 ± 4.06	23.82 ± 36.55	< 0.001
Percentage change/baseline	Reduction of -83.2 % ± 28.0	Increase of +11.3 % ± 54.7	< 0.001
Second month	N =20*	N =16*	
Number of tonic-clonic seizures ± SD	5.15 ± 7.73	13.80 ± 7.33	<0.002
Percentage change/baseline	Reduction of -68.6 % ± 41.9	Increase of +7.37 % ± 37.64	<0.002

*calculated on patients who completed the study. Patients who stopped treatment were not taken into account: 1 in the stiripentol group; 4 in the placebo group.

A lower number of seizures during the first and second month compared with baseline was observed in the stiripentol group.

Dosages and assay of medicinal products: the mean dosage of stiripentol during the period of comparison was 49 ± 3 mg/kg/d (45-51) and the mean minimum steady-state plasma concentration was 10 ± 3.6 mg/L (6.0-18.8).

In the stiripentol group, despite a reduction in the doses of clobazam (reduction in the mean dosage of 0.50 ± 0.16 mg/kg/d to 0.38 ± 0.10 mg/kg/d), a significant increase in the trough plasma clobazam and norclobazam concentrations[6] ($p<0.001$) and a reduction in that of hydroxynorclobazam ($p<0.001$) were observed after 7 weeks of treatment by stiripentol combined with valproate and clobazam. An increase in the trough plasma concentration of sodium valproate was also observed ($p<0.05$).

It cannot therefore be excluded that the improved efficacy against seizures was due to an increase in the plasma concentrations of the combined antiepileptic drugs and in particular, clobazam.

3.1.2 STICLO Italy study[7]

This was an additional complementary study with an identical protocol to the STICLO France study. Twenty-three patients aged from 3 to 18 years, with SMEI that had begun before the age of 1 year and with at least 4 clonic or tonic-clonic seizures per month were enrolled and treated by sodium valproate and clobazam, combined with stiripentol (N=12) or placebo (N=11).

Results:

The average age of enrolled patients was 9.2 ± 3.6 years (range 3.7 - 15.5) in the stiripentol group and 8.7 ± 4.4 years (range 3.5 - 18.9) in the placebo group. The mean number of tonic-clonic seizures at baseline (first month) was 33.6 ± 28.2 (range 2.14-86.1) in the stiripentol group and 27.4 ± 28.6 (range 3.75-101) in the placebo group.

Primary endpoint: The number of responders with a reduction in the number of tonic-clonic seizures of at least 50% during the second month compared with baseline, was significantly higher in the stiripentol group (8/12) than in the placebo group (1/11) ($p = 0.009$).

Secondary endpoints:

Table 3: Change in the number of tonic-clonic seizures between the baseline and the end of the 2nd month

	Stiripentol (n = 11) *	Placebo (n = 9) *	Chi 2
No seizure	3	0	p=0.05
Reduction >50% < 100%	5	1	
Reduction <50%	3	7	
Increase <50%	0	0	
Increase > 50%	0	1	

*calculated on patients who completed the study. Patients who stopped treatment were not taken into account: 1 in the stiripentol group; 2 in the placebo group.

Three patients in the stiripentol group had no tonic-clonic seizures during the two months of treatment versus no patient in the placebo group.

6 Values of plasma concentrations in mg/L normalised according to the dosage in mg/kg received by each patient.

7 Carried out between April 1999 and October 2000, cited in CHIRON C. Stiripentol - Neurotherapeutics, 2007, Vol. 4 (1): 123-125 and study report.

Table 4: Number of tonic-clonic seizures and change compared with baseline

	Stiripentol	Placebo	p (Mann and Whitney)
Initial phase (calculated for 30 days)	N=12	N=11	
Number of tonic-clonic seizures ± SD	33.6 ± 28.2	27.4 ± 28.6	NS
First month			
Number of tonic-clonic seizures ± SD	4.7 ± 7.3	29.0 ± 35.6	=0.0003
Percentage change/baseline	Reduction of -89.5 % ± 15.7	Increase of +5.5 % ± 55.4	< 0.05
Second month	N=11*	N=9*	
Number of tonic-clonic seizures ± SD	9.8 ± 10.0	16.7± 11.3	NS
Percentage change/baseline	Reduction of -74.3 % ± 26.3	Reduction of -12.7% ± 61.9	NS

*calculated on patients who completed the study. Patients who stopped treatment were not taken into account: 1 in the stiripentol group; 2 in the placebo group.

A smaller number of seizures were observed in the stiripentol group during the first month compared with baseline. This difference with the placebo group was not confirmed during the second month.

Dosages and assay of medicinal products: The mean dosage of stiripentol was 50.6 ± 4.2 mg/kg/d (43.1-58.3) and the mean trough steady-state plasma concentration was 10.2 ± 2.98 mg/L (5.70-14.0) after 7 weeks of treatment.

Despite a reduction in the doses of clobazam administered, the norclobazam concentration after 7 weeks of treatment increased in the stiripentol group.

It cannot be excluded that the improved efficacy against seizures was due to an increase in the plasma concentrations of the combined antiepileptic drugs and in particular, clobazam

3.2. Adverse effects

3.2.1 STICLO studies

STICLO Study France

Treatment discontinuations: 1 status epilepticus in the stiripentol group; 1 status epilepticus, 2 cases of lack of improvement and 1 case of drowsiness/motor deficiency in the placebo group leading to treatment discontinuation.

Adverse effects: at least one adverse event was reported in 21 patients in the stiripentol group versus 5/20 in the placebo group with, in particular, a higher number of events concerning the central nervous system (19 in the stiripentol group versus 5 in the placebo group).

The main adverse reactions reported were as follows:

- In the stiripentol group, CNS disorders: drowsiness (15), hyperexcitability (5), aggressiveness (3), ataxia (3), tremors (3), insomnia/nightmares (2), hypotonia (2), dysarthria (2) and gastrointestinal disorders: loss of appetite (7), weight loss (6), weight gain (5), abdominal pain (2), nausea/vomiting (2).
  Neutropenia (3), thrombocytopenia (2) and eosinophilia were also reported.
- In the placebo group, the main events reported were weight gain (4) and drowsiness (2).

  The reduction in the dosage of clobazam and/or sodium valproate led to the disappearance or regression of the adverse reactions in 6 patients out of 11 in the stiripentol group (no improvement: 2 cases, information not available: 3 cases) and 1 out of 3 in the placebo group (information not available: 2 cases).

STICLO Italy study
Treatment discontinuations: 1 case of drowsiness and postural instability in the stiripentol group, 1 worsening and 1 lack of improvement in the placebo group leading to treatment discontinuation.
Adverse reactions: at least one adverse reaction was reported in 9 patients in the stiripentol group and 2 in the placebo group. The events reported were mainly:

- In the stiripentol group: central nervous system disorders: drowsiness (7), hypotonia (3), hyperexcitability/agitation (2), irritability (2), ataxia (1), hyperkinesia (1), postural instability (1) and gastrointestinal disorders: loss of appetite (6), weight loss (2), nausea, vomiting (3) abdominal pain (1), and sialorrhoea (2)
- In the placebo group: ataxia (2), hyperkinesia (2), hyperexcitability (1), irritability (1), drowsiness (1), loss of appetite (1), and tremors (1).

3.2.2 TUA (temporary authorization of use)

Periodic safety update report on the 250 cases of the cohort TUA
Forty-one patients in the TUA cohort reported at least one adverse reaction including 15 serious reactions: sudden deaths unrelated to the product (4), repeated seizures (2), generalised status epilepticus (1), hepatic disorders (3), anorexia (3), weight loss (2), deterioration in general health status (2), drowsiness (3), and aggressiveness (1).

In 13 patients, DIACOMIT treatment was stopped for one of the following reasons: deaths unrelated to treatment (4), poor safety (5), lack of efficacy (2), change of therapeutic strategy (1) error in diagnosis (1).

Individual TUA: 1 case of drowsiness and postural instability and 1 case of generalised oedema related to the use of DIACOMIT were reported.

3.2.3 SmPC

The very common (≥ 1/10) or common (≥ 1/100, <1/10) adverse effects described with DIACOMIT are as follows:

- psychiatric and nervous system disorders: insomnia, aggressiveness, irritability, behaviour disorders, opposing behaviour, hyperexcitability, sleep disorders, drowsiness, ataxia, hypotonia, dystonia, and hyperkinesias.
- metabolism and nutrition disorders: anorexia, loss of appetite, and weight loss (especially when combined with sodium valproate).
- blood disorders: neutropenia. Persistent severe neutropenia that usually resolves spontaneously when DIACOMIT is stopped.
- nausea, vomiting.
- Raise of gamma GT (notably when combined with carbamazepine and sodium valproate).

Many of the above adverse reactions are often due to an increase in the plasma concentrations of other anticonvulsant medications and may resolve after a reduction in the dose of these products.

A European risk management plan has been set up in particular to monitor gastrointestinal and neurological disorders, neutropenia, the hepatotoxic potential and impact on psychomotor development.

3.3. Conclusion

The efficacy and safety of DIACOMIT were evaluated in combination with sodium valproate and clobazam in two phase III studies versus placebo in patients aged over 3 years with severe myoclonic epilepsy in infancy, not adequately controlled by a sodium valproate/clobazam combination.

The number of patients responding to DIACOMIT (reduction of at least 50% in the incidence of generalised tonic-clonic seizures) combined with valproate/clobazam was 15 out of 21 in the STICLO France study and 8 out of 12 in the STICLO Italy study.

The French Transparency Committee has no long-term efficacy and safety data[8] for DIACOMIT combined with clobazam and sodium valproate. The impact of treatment on psychomotor development cannot therefore be assessed.

Efficacy and safety data comparing DIACOMIT with another treatment combined with valproate and clobazam are not currently available.

Likewise, DIACOMIT as monotherapy or in combination with other antiepileptics than the valproate-clobazam combination has not been evaluated in SMEI.

The main adverse effects observed with DIACOMIT combined with valproate and clobazam concern the central nervous system: drowsiness, behavioural disorders (hyperexcitability, aggressiveness, and irritability), neurological disorders (ataxia, tremors, hypotonia, and dysarthria) and the gastrointestinal system: loss of appetite, weight loss or gain, abdominal pain, nausea, and vomiting.

In view of the protocol of the available studies, and in particular the fact that the valproic acid and clobazam concentrations were not strictly identical in the two groups, it cannot be excluded that the improved efficacy against seizures was due to increased plasma concentrations of the combined antiepileptics and in particular, clobazam. Results evaluating DIACOMIT versus placebo, combined with sodium valproate and clobazam, for 12 weeks at the maximum tolerated doses, in patients aged 6 months to 15 years with SMEI, are expected (2nd six months of 2009) within the scope of the conditional MA.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

Severe myoclonic epilepsy in infancy[9] is a rare and serious form of epilepsy in children, which begins during the first year of life and causes convulsive seizures that are difficult to control with currently available antiepileptic medications.

SMEI causes a considerable delay in psychomotor development and a marked deterioration in quality of life[10].

DIACOMIT combined with sodium valproate and clobazam is intended for symptomatic treatment when generalised tonic-clonic seizures are inadequately controlled by this combination.

DIACOMIT is used as a last-line therapy.
Its efficacy/safety ratio is high.

There are alternative treatments. However none is specifically indicated in severe myoclonic epilepsy in infancy.

8 CHMP Guidelines: at least 12 weeks.

9 Proposal for revised classification of epilepsies and epileptic syndromes. Commission on classification and terminology of the international league against epilepsy - Epilepsia, 30 (4), 389-399, 1989

10 Severe prognosis with a mortality rate by sudden or accidental death evaluated at 16%, (Dravet, 2002; Guerrini, 2006).

Public health benefit:
The burden corresponding to patients with generalised tonic-clonic convulsions caused by SMEI is low because of the small number of patients concerned.
Insofar as severe myoclonic epilepsy in infancy is a rare disease causing considerable disability for which there are only a few, inadequate alternative therapies, a public health need does exist.
A review of available data (no direct comparison, very limited duration of the studies making it impossible to assess the impact on psychomotor development, small sample sizes) and expected data[11] show that it is impossible to quantify the expected impact of this proprietary medicine on morbidity and quality of life.
Consequently, in the current state of knowledge, DIACOMIT is not expected to benefit public health benefit in this indication.

The actual benefit of DIACOMIT is substantial.

4.2. Improvement in actual benefit

DIACOMIT provides a moderate (level III) improvement in actual benefit in the management of patients with severe myoclonic epilepsy in infancy when the sodium valproate-clobazam combination does not provide adequate control.

4.3. Therapeutic use

Severe myoclonic epilepsy in infancy is characterised by the onset of prolonged refractory convulsions during the first year of life, in the form of generalised or unilateral clonic or tonic-clonic seizures, generally alternating from one side to the other. The first seizures are often triggered by a fever, infection or vaccination and resemble very early febrile convulsions. These convulsive seizures then become more frequent during the first two years of the illness and remain easily triggered by fever or light. During episodes of fever, seizures are often very long, of the status epilepticus type, or occur together in series. Later, myoclonic, atypical absence and partial seizures may occur whereas the frequency of status epilepticus seizures gradually subsides. Psychomotor retardation occurs during the second year of life, mainly involving language and is associated with ataxia[12,13,14].

The objective of treatment of SMEI is to reduce the frequency and severity of convulsive seizures by combining long-term anticonvulsant treatment and a treatment for convulsive seizures, an antipyretic treatment where necessary and prophylaxis for hyperthermia[15]. SMEI resists most antiepileptics and may be worsened by some of them[4,5] (carbamazepine, lamotrigine, phenytoin, vigabatrin, and phenobarbital).

Guidelines[16] for the management of drug-resistant partial epilepsy (2004, consensus), underline the importance of regular reassessment of drug-resistant epilepsy in specialised centres, because of the difficulties in diagnosis due to brain development and a possible rapid worsening.

The choice of drugs with an MA for treatment in children is restricted, in particular before the age of 2 years, taking into account the few studies performed in this age group.

No antiepileptic is specifically indicated for monotherapy or bitherapy in the treatment of generalised tonic-clonic convulsions in patients with severe myoclonic epilepsy in infancy.

11 Conditional MA: pending the results of a controlled clinical study of stiripentol in combination with clobazam + sodium valproate at maximum tolerated doses (2nd semester 2009) to ensure the "*per se* efficacy" of stiripentol.
12 Proposal for revised classification of epilepsies and epileptic syndromes. Commission on classification and terminology of the international league against epilepsy - Epilepsia, 30 (4), 389-399, 1989
13 DRAVET C. et al, Epilepsie myoclonique sévère du nourrisson – in: Les syndromes épileptiques de l'enfant et de l'adolescent – John Libbey Eurotext Ltd., 1984, (7): 58-66
14 NGYUEN THANH T. et al, Efficacité et tolérance à long terme du stiripentol dans le traitement de l'épilepsie myoclonique sévère du nourrisson (syndrome de Dravet) – Archives de Pédiatrie, 2002, 9: 1120-1127
15 CEULEMANS B. et al, Severe myoclonic epilepsy in infancy: Relevance for the clinician of severe epilepsy starting in infancy – Acta Neurol. Belg., 2004, 104: 95-99
16 ANAES – Consensus conference: Prise en charge des épilepsies partielles pharmaco-résistantes 3-4 March 2004.

Sodium valproate is recommended as monotherapy for first-line treatment, or in combination with another antiepileptic for second-line therapy[17]: benzodiazepines and in particular, clobazam are used[18] . When bitherapy is not sufficient, the addition of another antiepileptic may be considered.

Therapeutic use of DIACOMIT:
DIACOMIT is a treatment which in conjunction with clobazam and sodium valproate reduces the incidence of generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy whose seizures are not adequately controlled with clobazam and valproate.

To date, no other antiepileptic is specifically indicated with this combination and in this form of epilepsy. However, it cannot be excluded that the efficacy against seizures is due to increased plasma concentrations of the other antiepileptics given in combination and in particular, clobazam.

Controlled studies on DIACOMIT were carried out in children aged over 3 years. The clinical decision to use DIACOMIT in children aged less than 3 with SMEI must be made on an individual patient basis; by taking into account the potential benefits and clinical risks. In these younger children, adjunctive treatment by DIACOMIT should only be instituted after clinical confirmation of the diagnosis of SMEI. There are few data on the use of DIACOMIT in children aged less than 12 months.

4.4. Target population

Severe myoclonic epilepsy in infancy is a rare disease which concerns between 1/20,000 and 1/40,000 children[19,20] i.e. approximately 360 to 720 patients aged from 0 to 18 years (INSEE, 2006).

According to another approach, severe myoclonic epilepsy in infancy concerns approximately 1% of cases of epilepsy in children[21], i.e. on the basis of a prevalence of epilepsy in children ranging from $3.6^{0}/_{00}$ to $6.5^{0}/_{00}$, the number of children (from 0 to 18 years, INSEE 2006) likely to be affected by severe myoclonic epilepsy in infancy may be estimated to be between 520 and 950 patients.

There are no data about the number of adults or the proportion of patients with severe myoclonic epilepsy in infancy with tonic-clonic convulsions inadequately controlled by the sodium valproate/clobazam combination.

Therefore, it is difficult to estimate the target population that may potentially benefit from DIACOMIT from these figures.

4.5. Transparency Committee Recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the posology of the Marketing Authorisation.

4.5.1 Packaging: Appropriate to the conditions of prescription.

4.5.2 Reimbursement rate: 65 %

17 KORFF C.M. et al, Epilepsy syndromes in infancy – Pediatric Neurology, 2006, 34(4): 253-263
18 DRAVET C. et al, Severe myoclonic epilepsy in infancy: Dravet syndrome – Adv. Neuro., 2005.95:71-102
19 HURST D.L., Epidemiology of severe myoclonic epilepsy in infancy - Epilepsia, 1990.31(4): 397-400
20 YACOUB M, Brain and development, vol 14, N°5, 1992
21 GUERRINI R., Epilepsy in children - The Lancet, 2006; 367: 499-524