HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 February 2009

INOVELON 100 mg, film-coated tablet
Box of 10 tablets (CIP: 382 846-1 or 34009 382 846 1 4)

INOVELON 200 mg, film-coated tablet
Box of 60 tablets (CIP: 381 761-2 or 34009 381,761 2 4)

INOVELON 400 mg, film-coated tablet
Box of 60 tablets (CIP: 381 762-9 or 34009 381,762 2 2)

Applicant: EISAI SAS

Rufinamide

ATC Code: N03AF03

List 1
Orphan drug
May only be prescribed by specialists in paediatrics or neurology

Date of Marketing Authorisation (centralised procedure): 16/01/2007

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

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Rufinamide

1.2. Indication

"Inovelon is indicated as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients aged 4 years and older."

1.3. Dosage (see SPC)

"Treatment with Inovelon must be initiated by a physician specialised in paediatrics or neurology with experience in the treatment of epilepsy.

Inovelon is administered orally. It must be taken twice daily with water in the morning and in the evening, in two equally divided doses. As a food effect was observed, it will be preferable to administer Inovelon with food (see the Pharmacokinetic properties section of the SPC). If the patient has difficulty with swallowing, tablets can be crushed and administered in half a glass of water.

Use in children aged four years and older and less than 30 kg
Patients < 30 kg not receiving valproate:
Treatment should be initiated at a daily dose of 200 mg. According to clinical response and tolerability, the dose may be increased by 200 mg/day increments, as frequently as every two days, up to a maximum recommended dose of 1,000 mg/day. Doses of up to 3,600 mg/day have been evaluated in a limited number of patients.
Patients < 30 kg also receiving valproate medication:
As valproate significantly decreases clearance of Inovelon, a lower maximum dose of Inovelon is recommended for patients < 30 kg being co-administered with valproate. Treatment must be initiated at a daily dose of 200 mg. According to clinical response and tolerability, after a minimum of two days the dose may be increased by 200 mg/day increments, up to a maximum recommended dose of 600 mg/day.

Use in adults and children aged four years and older and of 30 kg or over
Treatment must be initiated at a daily dose of 400 mg. According to clinical response and tolerability, the dose may be increased by 400 mg/day increments, every two days, up to a maximum recommended dose as indicated in the table below.

Body weight	30.0 – 50.0 kg	50.1 – 70.0 kg	≥ 70.1 kg
Maximum recommended dose (mg/day)	1800	2400	3200

Doses of up to 4,000 mg/day (body weight 30-50 kg) or 4,800 mg/day (body weight over 50 kg) have been studied in a limited number of patients.

Elderly patients
There is limited data available on the use of Inovelon in elderly patients. Since the pharmacokinetic parameters of rufinamide are not altered in elderly patients (see the Pharmacokinetic properties section of the SPC), dosage adjustment is not required in patients over 65 years of age.

Patients with renal impairment
A study carried out in patients with severe renal impairment indicated that no dose adjustments are required for these patients (see the Pharmacokinetic properties section of the SPC).

Patients with hepatic impairment
The use of this product in patients with hepatic impairment has not been studied. Caution and careful dose increase is recommended with treating patients with mild to moderate hepatic impairment. Use in patients with severe hepatic impairment is not recommended.

Effect of food
Inovelon should preferably be taken with food (see the Pharmacokinetic properties section of the SPC).

Discontinuation of Inovelon treatment
Discontinuation of treatment must be gradual. In clinical trials, Inovelon treatment was discontinued by reducing the dose by approximately 25% every two days.

If one or more doses are forgotten an individual clinical assessment is necessary.

Uncontrolled open-label studies suggest sustained long-term efficacy, although no controlled study has been conducted for longer than three months."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

N:	nervous system
N03:	antiepileptics
N03A:	antiepileptics
N03AF:	carboxamide derivatives
N03AF03:	rufinamide

2.2. Medicines in the same therapeutic category

None.

2.3. Medicines with the same therapeutic aim (see SPC for indications)

Valproic acid - DEPAKINE
Adults and children:
Either as monotherapy or in combination with another antiepileptic treatment:

- Treatment of generalised epilepsy: clonic, tonic and tonicoclonic seizures, absences, myoclonic and atonic seizures, and **Lennox-Gastaut syndrome**.
- Treatment of partial epilepsy: partial seizures with or without secondary generalisation.

Children:

Prevention of seizure relapse after one or more febrile convulsions, presenting complex febrile convulsion criteria, where intermittent benzodiazepine prophylaxis is ineffective.

Lamotrigine - LAMICTAL

Adults and children over 12:

Either as monotherapy or in combination with another antiepileptic treatment:

- Treatment of generalised epilepsy: clonic, tonic and tonicoclonic seizures, absences, myoclonic and atonic seizures, **Lennox-Gastaut syndrome**.
- Treatment of partial epilepsy: partial seizures with or without secondary generalisation.

Children aged 2 to 12:

In combination with another antiepileptic treatment when the latter is not sufficiently effective:

- Treatment of generalised epilepsy: clonic, tonic and tonicoclonic seizures, absences, myoclonic and atonic seizures, **Lennox-Gastaut syndrome**.
- Treatment of partial epilepsy: partial seizures with or without secondary generalisation.

Felbamate - TALOXA

Taloxa is not indicated as a first-line treatment for epilepsy. It can be prescribed for the following indication after a thorough assessment of the risk/benefit ratio, taking account of the risk of haematological toxicity, especially medullar aplasia, and of severe hepatotoxicity. The potential risk associated with the use of Taloxa must be weighed up against the risks associated with the lack of appropriate medical treatment.

Lennox-Gastaut syndrome: To complement prior treatment, to treat Lennox-Gastaut syndrome in adults and children aged over 4 that is not controlled by other appropriate antiepileptics available.

Clobazam - URBANYL

10-mg and 20-mg tablets:

Adults and children:

In combination with other antiepileptic treatment, in adults and children:

- Treatment of generalised epilepsy: clonic, tonic and tonicoclonic seizures, absences, myoclonic and atonic seizures, infantile spasms and **Lennox-Gastaut syndrome**.
- Treatment of partial epilepsy: partial seizures with or without secondary generalisation.

Clonazepam - RIVOTRIL

Tablets (adults and children) and oral solution (children):

Treatment of epilepsy, either as temporary monotherapy or in combination with another antiepileptic treatment:

- Treatment of generalised epilepsy: clonic, tonic and tonicoclonic seizures, absences, myoclonic and atonic seizures, infantile spasms and **Lennox-Gastaut syndrome**.
- Treatment of partial epilepsy: partial seizures with or without secondary generalisation.

Solution for injection (adults and children):
Emergency treatment for status epilepticus.

Topiramate – EPITOMAX
Adults and children aged 2 and over:
Treatment of generalised epilepsy (clonic, tonic and tonicoclonic seizures) and partial epilepsy (partial seizures with or without generalisation):

- as monotherapy after a previous treatment has failed,
- in combination with other antiepileptic treatments when the latter are insufficiently effective.

EPITOMAX has not been granted marketing authorisation for **Lennox-Gastaut syndrome**.

Levetiracetam – KEPPRA

- Keppra is indicated as monotherapy in the treatment of partial seizures with or without secondary generalisation in patients aged 16 or over recently diagnosed with epilepsy.
- Keppra is indicated in combination with other drugs:
    - in the treatment of partial seizures with or without secondary generalisation in adults and children aged 4 and over with epilepsy;
    - in the treatment of myoclonic seizures in adults and adolescents aged 12 or over with juvenile myoclonic epilepsy;
    - in the treatment of generalised primary tonicoclonic seizures in adults and adolescents aged 12 or over with generalised idiopathic epilepsy.

KEPPRA has not been granted marketing authorisation for **Lennox-Gastaut syndrome**.

3. ANALYSIS OF AVAILABLE DATA

Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy with childhood onset, which normally develops between the ages of 3 and 5. LGS is characterised by the following triad of symptoms: various epileptic seizures (atypical absences, axial tonic seizures and sudden atonic or myoclonic falls); a specific electroencephalogram (EEG) reading with a slow (<3 Hz), diffuse, interictal spike-and-wave pattern when the subject is awake and rapid rhythms (10 Hz) when the subject is asleep; slow mental development and personality disorders. The most common clinical manifestations are tonic seizures (17-92%), atonic seizures (26-56%) and atypical absences (20-65%)[1].

[1] Campos-Castello J. Lennox-Gastaut syndrome. Orphanet Encyclopedia, September 2004.

3.1. Efficacy

The efficacy and tolerability of rufinamide were assessed versus placebo in a double-blind phase III randomised study **(study 022[2])** investigating adjunvant treatment of epileptic seizures associated with LGS[3]. The study was conducted between March 1998 and September 2000 in 36 paediatric neurology centres in nine countries.

Methodology

Following a 28-day pre-inclusion phase, 139 patients were randomised for an 84-day double-blind period: rufinamide (n=75), placebo (n=64).
Treatment, given orally twice a day, was initiated at a dose of 10 mg/kg/d and increased during the 14-day titration period up to a maximum of 45 mg/kg/d.

The inclusion criteria for patients taking part in the study were:
- age between 4 and 30;
- treatment with 1 to 3 antiepileptics at a fixed dose during the 28-day pre-inclusion period;
- at least 90 seizures in the month preceding the pre-inclusion period;
- an EEG within the past six months showing a slow spike-and-wave pattern;

The main endpoints were:
- change[4] in the overall frequency of epileptic seizures over a 28-day period between the pre-inclusion phase and the double-blind phase (E1);
- change[4] in the frequency of tonic/atonic seizures ("drop attacks") over a 28-day period between the pre-inclusion phase and the double-blind phase (E2);
- change in the severity of seizures based on the overall assessment of the patient's condition by a parent at the end of the double-blind phase. This is expressed as a score on a seven-point scale. A score of 0 indicates no change in severity, a score of +3 indicates a clear improvement and a score of -3 indicates a pronounced deterioration compared to the initial situation (E3).

Rufinamide was considered effective if the percentage reduction in the overall frequency of seizures (E1) and/or a lower figure for the endpoints E2 and E3 were significantly superior compared to the placebo.

Details of some of the secondary endpoints (the percentage of responders, i.e. patients with a reduction of at least 50% in the frequency of tonic/atonic seizures over 28 days; and a composite score for the patient's overall condition reflecting the total of five scores on a seven-point scale measured by a parent (alertness, interaction with the environment, performance in everyday activities, responsiveness to questions, severity of seizures)) are given below.

Results

Of the 139 patients who were randomised, 138 (M: 86, F: 52, average age: 14) received the treatment on a double-blind basis (one of the patients in the rufinamide group did not receive the treatment due to an administrative error).

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[2] Glauser T., Kluger G., Sachdeo R., Krauss G., Perdomo C., Arroyo S. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology, 2008; 70: 1950-58.

[3] Defined according to the criteria of the International League Against Epilepsy Classification

[4] The frequency of seizures occurring during the double-blind phase is expressed as the average frequency of seizures over 28 days. The change in the frequency of seizures in percentage terms is: 100. (T-B)/B, where T and B represent the frequency of seizures over 28 days in the double-blind phase and the pre-inclusion phase respectively.

Table 1. Age breakdown of the patients in the two treatment arms

Age (years)	Rufinamide (n=74)	Placebo (n=64)
median	13.0 (4.0-35.0)	10.5 (4.0-37.0)
4 –12, n (%)	31 (41.9)	33 (51.6)
12 -17, n (%)	19 (25.7)	17 (26.6)
>17, n (%)	24 (32.4)	14 (21.9)

Table 2. Concomitant treatments: number of antiepileptics per patient

Number	Rufinamide (n=74)		Placebo (n=64)	
	n	%	N	%
1	8	10.8	8	12.5
2	38	51.4	35	54.7
3	28	37.8	21	32.8

Table 3. Antiepileptics taken by at least 10% of patients

Antiepileptic	Rufinamide (N=74)		Placebo (N=64)	
	n	%	n	%
Valproate	44	59.5	35	54.7
Lamotrigine	30	40.5	19	29.7
Topiramate	20	27.0	17	26.6
Clonazepam	14	18.9	7	10.9
Carbamazepine	12	16.2	12	18.8
Clobazam	10	13.5	8	12.5
Phenytoin	10	13.5	12	18.8
Phenobarbital	6	8.1	9	14.1

Table 4. Premature termination of treatment

	Rufinamide (n=74)	Placebo (n=64)
Premature termination	10 (13.5%)	5 (7.8%)
▪ adverse events	6	-
▪ unsatisfactory therapeutic effect	3	1
▪ consent withdrawn	1	1
▪ violation of protocol	-	2
▪ administrative problem	-	1

65 patients (87.8%) reached a dose of approximately 45 mg/kg/d; this took about 7 days for 50 of these patients (76.9%) and about 14 days for the other 15 (23.1%). The average dose after the one- or two-week titration phase was 1,700 mg/day. Over 87% of patients had at least 12 weeks treatment in both arms.

a) Efficacy

The tables below show the frequency of seizures of any type, of tonic/atonic seizures and the seizure severity scores:

Table 5. Change in the frequency of epileptic seizures of any type over 28 days (ITT)

Number of seizures over 28 days	Rufinamide			Placebo		
	n	Median	Extended	n	Median	Extended
reference period	74	**290.0**	(48 - 53760)	64	**205.0**	(21 - 109714)
double-blind phase	74	204.1	(5 - 43262)	64	205.4	(51 - 113165)
change in number of seizures* (%)	74	**-32.7**	(-92 - 381)	64	**-11.7**	(-83 - 551)

* p = 0.0015 - Wilcoxon test

Table 6. Change in the frequency of tonic/atonic seizures over 28 days (ITT)

Number of tonic/atonic seizures over 28 days	Rufinamide			Placebo		
	n[a]	Median	Extended	n[a]	Median	Extended
reference period	73	92.0	(5 - 14304)	60	92.5	(1 - 13122)
double-blind phase	73	60.7	(0 - 12036)	60	76.2	(0 - 17500)
change in number of seizures* (%)	73	**-42.5**	(-100 - 1191)	60	**+1.4**	(-100 - 710)

* $p < 0.0001$ according to Wilcoxon
[a] 5 patients (1 on rufinamide and 4 on placebo) had not had a tonic/atonic seizure during the inclusion phase

Table 7. Seizure severity score on the assessment of patients' overall condition sub-scale (ITT)

Severity of seizures	Rufinamide (n=73)		Placebo (n=62)	
	n[a]	%	n[a]	%
Very marked deterioration	0	0.0	0	0.0
Marked deterioration	3	4.1	4	6.5
Slight deterioration	3	4.1	4	6.5
No change	28	38.4	35	56.5
Slight improvement	14	19.2	10	16.1
Marked improvement	16	21.9	8	12.9
Very marked improvement	9	12.3	1	1.6

[a] 3 patients (1 on rufinamide and 2 on placebo) did not have the intensity of their seizure assessed

An improvement in the intensity of seizures (very marked, marked or slight) was observed in 39 patients (53.4%) on rufinamide versus 19 patients (30.6%) on placebo ($p = 0.0041$).
The percentage of responders was higher in the rufinamide group than in the placebo group for any type of seizure (31.1% vs 10.9% on placebo) and for tonic-atonic seizures (42.5% vs 16.7%). However, the percentage of patients no longer experiencing tonic-atonic seizures at all was low and no difference between the two groups was observed (4.1% vs 3.3%). No subjects remained seizure-free during the study.

No difference between the two groups was observed with regard to the composite score for the overall assessment of the patient's condition.

b) Tolerability
60 patients (81.1%) in the rufinamide group reported at least one adverse event versus 52 (81.3%) in the placebo group.

The most frequent adverse events (> 10%) were:
- drowsiness (24.3% in the rufinamide group versus 12.5% in the placebo group);
- vomiting (21.6% vs 6.3%);
- fever (13.5% vs 17.2%);
- diarrhoea (5.4% vs 10.9%).

Serious, non-fatal adverse events were reported after the start of the double-blind phase for two patients in the rufinamide group (diarrhoea, upper respiratory infection and vomiting in one case and rash, fatigue and vomiting in the other) and two patients in the placebo group (sinusitis and petit mal).

Six patients in the rufinamide group (vs. non in the placebo group) discontinued treatment as a result of adverse events (five children and one adult): one because of serious adverse events (rash, fatigue and vomiting) and five because of minor adverse events. The most common adverse events leading to discontinuation of treatment were vomiting (n=3), drowsiness (n=2) and skin rash (n=2). Three of these patients discontinued treatment in the first three weeks. Three patients in the rufinamide group were reported as having status epilepticus (none in the placebo group).

Cognitive/psychiatric adverse events occurred in a smaller percentage of patients in the rufinamide group (17.6%) than in the placebo group (23.4%). The adverse events most frequently reported were psychomotor agitation (3 patients) in the rufinamide group and aggression, lethargy and insomnia (3 patients in each case) in the placebo group.

A slight increase in TSH occurred in 12.5% of the patients taking rufinamide and 4.2% of the patients on placebo, but no change in thyroxine levels was observed.

Open-label extension phase

All the patients who completed the 84-day double-blind phase of study 022 were suitable for rufinamide treatment during an open-label extension phase. Treatment was initiated during a 14-day titration period on patients who had previously been taking the placebo. 124 (89%) of the 139 patients randomised in study 022 were monitored during this phase, which continued until the product was launched onto the market in the relevant country.

The median length of exposure to rufinamide was 432 days (10 to 1,149 days). Approximately 60% of patients (74/124) were treated with rufinamide for 18 months or more and 40% (51/124) were treated for 2 years or more. Three patients were given rufinamide for at least 3.5 years.

The effect of rufinamide on reducing the frequency of seizures continued during the extension phase. Patients who had previously been on placebo during the double-blind phase experienced less frequent epileptic seizures when being treated with rufinamide.

Regarding the response rate, 45% (55/122) and 41% (50/122) of patients responded during the final 6 and 12 months of treatment. Two of the 122 patients (1.6%) had no seizures during the final 6 months of treatment.

42 patients (33.9%) continued the study until its conclusion, i.e. they received rufinamide for 44 months. Of the 82 patients who discontinued treatment prematurely, 51 (41%) did so because the therapeutic effect was inadequate and 12 (9.7%) due to adverse events. 113 patients (over 90%) experienced at least one adverse event. The adverse events most commonly reported were vomiting (30.6%), fever (25.8%), upper respiratory tract infections (21.8%) and drowsiness (21.0%). Two patients died, but their deaths were regarded as not being attributable to treatment.

Conclusion

The total frequency of seizures, the frequency of tonic-atonic seizures and the severity of seizures were all lower in the rufinamide group than in the placebo group. However, it should be noted that there was a significant difference between the two groups with regard to the median figures for the total frequency of seizures during the pre-inclusion phase (290 in the rufinamide group versus 205 in the placebo group). However, as some seizures (absences, partial seizures) can pass unnoticed, change in the frequency of tonic-atonic seizures is a more reliable endpoint than the total number of seizures (endpoint E1).

The rufinamide titration phase, obtained in 7 to 14 days for most patients in the rufinamide group, can be regarded as fast and is a beneficial impact in the management of epileptic seizures.

3.2. Tolerance

3.2.1. Outcome of clinical trials

It is estimated that 1,875 epilepsy patients have been treated in the context of double-blind studies: 1,240 patients with rufinamide and 635 patients with placebo.
The most frequent adverse events (frequency > 10%) were:

- Headache (rufinamide: 22.9% vs placebo: 18.9%)
- Vertigo (rufinamide: 15.5% vs placebo: 9.4%)
- Fatigue (rufinamide: 13.6% vs placebo: 9.0%)
- Drowsiness (rufinamide: 11.8% vs placebo: 9.1%)
- Nausea (rufinamide: 11.4% vs placebo: 7.6%)

In addition, 18.7% of patients who had at least one dose of rufinamide experienced eye problems (particularly diplopia and blurred vision).

The number of serious adverse events reported was 98 in 78 patients (6.3%) in the rufinamide group and 28 in 25 patients (3.9%) in the placebo group. In the rufinamide group, these events were general disorders, eye problems and epileptic seizures, with four cases of status epilepticus (none in the placebo group).
7 to 8% of patients in the rufinamide group discontinued treatment because of adverse events (the adverse events most frequently involved were vertigo, fatigue, headache, nausea and diplopia) versus 0 to 4.3% in the placebo group.

Among the 1,978 patients who received at least one dose of rufinamide in the context of clinical trials conducted into the treatment of epileptic seizures, either in isolation or in the context of LGS, 327 serious adverse events were recorded in 261 patients (13.2%). The events most frequently reported were linked to epilepsy: convulsions (n=43), status epilepticus (n=19), grand mal (n=11), partial seizures with secondary generalisation (n=8), complex partial seizures (n=4), simple partial seizures (n=1), and unidentified epileptic seizures (n=4). Pneumonia (n=15) and vomiting (n=11) also occurred. 13.1% of patients discontinued treatment because of adverse events (fatigue, headache, nausea, vertigo, convulsions, diplopia, drowsiness, rash and vomiting).

According to the SPC, the most frequently reported adverse events among the over 1,900 patients with various forms of epilepsy exposed to rufinamide were headache, vertigo, fatigue and drowsiness. Among patients suffering from LGS, drowsiness and vomiting were the most frequently observed adverse effects. The intensity of the adverse effects was generally slight to moderate.

None of the deaths which occurred during treatment was attributed to rufinamide.

3.2.2. Outcome of pharmacovigilance

The first periodic report, covering the period from 16 January to 15 July 2007, had allowed a special warning to be added to the SPC following the shortening of the QTc interval caused by rufinamide which had been observed in a study carried out into monitoring the QT interval.

No change was made to the product's tolerance profile as a result of data from the second periodic pharmacovigilance report (16/07/2007 - 15/01/2008). The number of patients exposed to rufinamide during this time is estimated at 108,776 patient-days. The number of patients exposed as part of clinical studies is estimated at 37,247 patient-days. 19 reports were submitted during this period, five of which related to serious events.

Furthermore, the company has submitted a risk management plan in which it undertook to monitor cases of status epilepticus, hypersensitivity, loss of appetite and weight loss, abnormal coordination, drowsiness, vertigo, diplopia and blurred vision, vomiting, as well as the occurrence of foetal malformation, the potential development of haematological dyscrasia, immunotoxicity, developmental and growth disorders in children and adolescents, cognitive adverse effects and the risk of suicide.

3.3. Conclusion

The efficacy of rufinamide as an adjuvant treatment for poorly controlled epileptic seizures associated with Lennox-Gastaut syndrome has been demonstrated in a randomised double-blind phase III study versus placebo. The 139 patients taking part, with an average age of 14, had to have been treated with 1 to 3 antiepileptics at a fixed dose for at least 28 consecutive days. Rufinamide administered orally for 84 days reduced the frequency of all seizures over periods of 28 days by 32.7% (vs 11.7%; p=0.0015) and the frequency of tonic-atonic seizures over periods of 28 days by 42.5% (vs an increase of 1.4%; p<0.0001) and reduced the severity of seizures in 53.4% of cases (vs 30.6%; p=0.0041). The open-label extension phase of this study suggests that the effect of rufinamide in terms of reducing the frequency of seizures persists. However, the high proportion of patients who terminated the study prematurely because of inadequate therapeutic effect (41%) means that resistance to the treatment cannot be excluded.

The most frequent adverse events that might be linked to the treatment affect the nervous system (headache, vertigo, fatigue, drowsiness) and the gastrointestinal system (vomiting, nausea). Eye problems such as diplopia and blurred vision were also observed. No dose/effect relationship was identified.

Pharmacovigilance is focusing particularly on cases of status epilepticus and antiepileptic hypersensitivity syndrome, as well as haematological disorders, instances of immunotoxicity, possible effects on learning, intellectual development, growth, endocrine function and puberty.

As the syndrome can affect children as young as two, the Committee regrets that the inclusion criteria did not allow children below the age of four to participate.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

LGS is one of the most serious epileptic syndromes affecting children. It is resistant to treatment and is often associated with mental retardation. The mortality rate is approximately 5%, though death is rarely due to the progress of the epilepsy itself but more often to intercurrent conditions or incidents associated with seizures[5, 6].

These proprietary products are intended for symptomatic treatment.

The efficacy/adverse effects ratio in this indication is high.

Therapeutic alternatives to these proprietary drugs exist.

Public health benefit:
Despite its severity (very severe form of epilepsy, neurocognitive handicap), Lennox-Gastaut syndrome constitutes a minor public health burden because of the small number of patients affected.

There is a public health need in that Lennox-Gastaut syndrome causes severe disability despite availability of existing treatments.

The impact on morbidity, mortality and the quality of life of these children is expected to be moderate at best in view of the clinical data available and the existing treatments.

However, as this syndrome is rare, no public health benefit is expected for this proprietary drug in this indication.

The actual benefit of these drugs is substantial.

4.2. Improvement in actual benefit

INOVELON offers a minor (level IV) improvement in actual benefit in the therapeutic management of patients aged 4 and over with Lennox-Gastaut syndrome that is resistant to first-line treatments.

[5] Source: www.orpha.net
[6] Genton P., Dravet C. Lennox-Gastaut syndrome. Chapter 241. Section 10 ; June 14, 2007 :2417-27.

4.3. Therapeutic use [7, 8, 9, 10]

Lennox-Gastaut syndrome is characterised by frequent resistance to treatments, especially conventional anti-epileptics. Selecting the most appropriate antiepileptic is a complex task given the lack of consensus, the fact that an antiepileptic may be effective in treating one type of seizure but aggravate another type of seizure, the frequent use of multiple therapies which increases the likelihood of adverse effects, and poor long-term efficacy.

Initial management of the syndrome involves the administration of broad-spectrum antiepileptics: valproic acid, either alone or in combination with benzodiazepines (this can lead to cognitive disorders which can aggravate the intellectual impairment associated with the syndrome) and lamotrigine (risks of skin damage). The valproic acid / lamotrigine combination is used as second-line treatment (increased risk of skin toxicity).

Patients who continue to experience tonic-atonic seizures despite being treated with a well-administered regimen of valproic acid / lamotrigine could benefit from also receiving rufinamide, which is a useful additional alternative treatment.

Other antiepileptics can be used in combination therapy:
- topiramate (risk of anorexia and cognitive disorders - this substance has not been granted marketing authorisation for Lennox-Gastaut syndrome);
- felbamate (risks of haematological toxicity, especially medullary aplasia, and severe hepatotoxicity);
- levetiracetam (little data - this substance has not been granted marketing authorisation for Lennox-Gastaut syndrome).

To control tonic and tonic-clonic seizures with a risk of aggravating other types of seizures: phenytoin, carbamazepine.
In some cases, to control absences: ethosuximide.

Corticosteroids and the corticotropic hormone can be used during initial management or occasionally when electroclinical aggravations occur.

Non-drug treatments for LGS are used in cases of drug-resistant epilepsy:
- Ketogenic diet
- Stimulation of the vagus nerve: beneficial in the symptomatic treatment of confirmed epilepsy, disabling and drug-resistant epilepsy where it has been decided that intracranial surgery is not appropriate.
- Surgery (callosotomy): a purely palliative therapeutic option, rarely suggested, considered as rescue treatment, justified in the case of patients in whom all drug treatments have failed.

[7] National Institute for Clinical Excellence. The epilepsies, the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Clinical Guideline 20, October 2004.

[8] Wheless J.W., Clarke D.F., Arzimanoglou A., Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disorder, 2007; 9(4): 353-412.

[9] Campos-Castello J. Lennox-Gastaut syndrome. Orphanet Encyclopedia, septembre 2004.

[10] Arzimanoglou A., French J., Blume WT. et al. Lennox-Gastaut syndrome : a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurology, 2009: 8:82-93.

4.4. Target Population

The prevalence of LGS is estimated at 15 in 100,000 individuals[11], i.e. 9,600 cases in France.
The expert consensus is that the sub-population of resistant patients who might benefit from treatment with rufinamide is not likely to exceed 3,000 patients in France.

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.

4.5.1 Packaging

An oral suspension form, required for young children, is currently being developed.

4.5.2 Reimbursement rate: 65%

[11] Prévalence des maladies rares : Données bibliographiques [Prevalence of rare diseases: Bibliographical data]. Les Cahiers d'Orphanet, série Maladies rares [Orphanet Publications, Rare diseases series]. November 2008, no. 1 (Available at www.orphanet.fr).