European Medicines Agency

Doc. Ref. EMEA/348643/2009
P/108/2009

EUROPEAN MEDICINES AGENCY DECISION

of 9 June 2009

on the agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the granting of a waiver for carisbamate (EMEA-000360-PIP01-08) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended

(ONLY THE ENGLISH TEXT IS AUTHENTIC)

DISCLAIMER: This Decision does not entitle to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006, as amended.

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THE EUROPEAN MEDICINES AGENCY,

Having regard to the Treaty establishing the European Community,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use as amended and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[2],

Having regard to the application submitted by Janssen Cilag International NV on 21 August 2008 under Article 16(1) also requesting a waiver under Article 13 of said Regulation and a deferral under Article 20 of said Regulation,

Having regard to the Opinion of the Paediatric Committee of the European Medicines Agency, issued on 30 April 2009, in accordance with Article 18 of Regulation (EC) No 1901/2006 as amended, and Article 13 of said Regulation and Article 21 of said Regulation,

Having regard to Article 25 of Regulation (EC) No 1901/2006 as amended,

WHEREAS:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the granting of a waiver,

(2) It is therefore appropriate to adopt a Decision granting a Paediatric Investigation Plan,

(3) It is therefore appropriate to adopt a Decision granting a deferral,

(4) It is therefore appropriate to adopt a Decision granting a waiver.

[1] OJ L 378, 27.12.2006, p.1
[2] OJ L 136, 30.4.2004, p. 1

HAS ADOPTED THIS DECISION:

Article 1

A Paediatric Investigation Plan for carisbamate, film-coated tablet, oral suspension, intravenous formulation, oral use, intravenous use, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

Article 2

A deferral for carisbamate, film-coated tablet, oral suspension, intravenous formulation, oral use, intravenous use, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

A waiver for carisbamate, film-coated tablet, oral suspension, intravenous formulation, oral use, intravenous use, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 4

This decision is addressed to Janssen Cilag NV International, Turnhoutseweg 30, B-2340, Beerse, Belgium.

Done at London, 9 June 2009

For the European Medicines Agency
Thomas Lönngren
Executive Director

(Signature on file)

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

Doc. Ref. EMEA/PDCO/248875/2009
EMEA-000360-PIP01-08

OPINION OF THE PAEDIATRIC COMMITTEE ON THE AGREEMENT OF A PAEDIATRIC INVESTIGATION PLAN AND A DEFERRAL AND A WAIVER

Scope of the application

Active substance(s):
Carisbamate

Condition(s):
- Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures
- Neonatal seizures
- Infantile spasms (West Syndrome)
- Lennox-Gastaut Syndrome
- Other paediatric epilepsy syndromes such as Dravet Syndrome, myoclonic astatic syndrome, epilepsy with continuous sharp-waves in sleep, idiopathic partial epilepsy, absence epilepsy

Pharmaceutical form(s):
Film-coated tablet
Oral suspension
Intravenous formulation

Route(s) of administration:
Oral use
Intravenous use

Name/corporate name of the PIP applicant:
Janssen Cilag International NV

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Janssen Cilag International NV submitted for agreement to the EMEA on 21 August 2008 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 25 September 2008.

Supplementary information was provided by the applicant on 17 February 2009.

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Opinion

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to agree the paediatric investigation plan in accordance with Article 18 of said Regulation,

- to grant a deferral in accordance with Article 21 of said Regulation,

- to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with

  Articles 11(1)(b) of said Regulation, on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified subset(s) of the paediatric population.

The Icelandic and the Norwegian Paediatric Committee member(s) agree(s) with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the agreed paediatric investigation plan and the subset(s) of the paediatric population and condition(s) covered by the waiver are set out in the Annex I.

This opinion is forwarded to the applicant and the Executive Director of the Agency, together with its annex(es) and appendix.

London, 30 April 2009

On behalf of the Paediatric Committee
Dr Daniel Brasseur, Chairman

(Signature on file)

ANNEX I

THE MEASURES AND TIMELINES OF THE AGREED PAEDIATRIC INVESTIGATION PLAN AND THE SUBSET(S) OF THE PAEDIATRIC POPULATION AND CONDITION(S) COVERED BY THE WAIVER

A. CONDITION(S)

- Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures
- Neonatal seizures
- Infantile spasms (West Syndrome)
- Lennox-Gastaut Syndrome
- Other paediatric epilepsy syndromes such as Dravet Syndrome, myoclonic astatic syndrome, epilepsy with continuous sharp-waves in sleep, idiopathic partial epilepsy, absence epilepsy

B. WAIVER

B.1 Condition

Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures,

The waiver applies to:

- Preterm newborn infants, Term newborn infants (from birth to less than 28 days) for film-coated tablet, oral suspension, oral use and intravenous formulation, intravenous use

on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

B.2 Condition

Neonatal seizures

The waiver applies to:

- Infants and toddlers (from 28 days to less than 24 months), Children (from 2 to less than 12 years), Adolescents (from 12 to less than 18 years) for film-coated tablet and oral suspension, oral use and intravenous formulation, intravenous use

on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

B.3 Condition

Infantile spasms (West Syndrome)

The waiver applies to:

- Preterm newborn infants, Term newborn infants (from birth to less than 28 days) for film-coated tablet, oral suspension, oral use and intravenous formulation, intravenous use

on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

B.4 Condition

Lennox-Gastaut Syndrome

The waiver applies to:

- Preterm newborn infants, Term newborn infants (from birth to less than 28 days) for film-coated tablet and oral suspension, oral use and intravenous formulation, intravenous use

on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

B.5 Condition

Other paediatric epilepsy syndromes such as Dravet Syndrome, myoclonic astatic syndrome, epilepsy with continuous sharp-waves in sleep, idiopathic partial epilepsy, absence epilepsy

The waiver applies to:

- Preterm newborn infants, Term newborn infants (from birth to less than 28 days) for film-coated tablet and oral suspension, oral use and intravenous formulation, intravenous use

on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

C. PAEDIATRIC INVESTIGATION PLAN

C.1 Condition to be investigated

Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures.

- **Proposed PIP indication**

Treatment of patients with localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures.

- **Subset(s) of the paediatric population concerned by the paediatric development**

From 1 month to less than 18 years.

- **Formulation(s)**

Film-coated tablet (100 mg, 200 mg, 400 mg)
Oral suspension (20 mg/ml)
Intravenous formulation to be developed

- **Studies**

Area	Number of studies	Description
Quality	3	Development of paediatric age-appropriate strengths of film-coated tablets. Development of an oral suspension. Development of an intravenous formulation.
Non-clinical	4	2- week dose range-finding toxicity study in juvenile rats. 39-day juvenile rat toxicity study. 2-week dose range-finding toxicity study in juvenile dogs. 20-day pharmacokinetic study in nursing rat pups.
Clinical	6	Open-label, single- and repeat-dose study to evaluate pharmacokinetics, safety, and tolerability of intravenously administered carisbamate in healthy adult subjects. Open-label, single- and multiple-dose, study to evaluate pharmacokinetics, safety, and tolerability of carisbamate as adjunctive therapy in children with epilepsy, aged 4 years to less than 16 years, followed by an open-label extension study (15 months). Open-label, single- and multiple-dose, study to evaluate pharmacokinetics, safety, and tolerability of carisbamate as adjunctive therapy in children with epilepsy, aged 1 month to less than 4 years, followed by an open-label extension study (15 months). Openlabel, multiple-dose study to evaluate pharmacokinetics, safety, and tolerability of intravenously administered carisbamate in patients with epilepsy aged 1 month to less than 18 years, with open label extension (15 months). Randomized, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy, safety, and tolerability of carisbamate (oral suspension and tablets) as adjunctive therapy in patients aged 4 years to less than 16 years with partial onset seizures, followed by an open-label extension (15 months). Randomized, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy, safety, and tolerability of carisbamate (oral suspension) as adjunctive therapy in patients aged 1 month to less than 4 years with partial onset seizures, followed by an open-label extension (15 months).

C.2 Condition to be investigated

Neonatal seizures

- **Proposed PIP indication**

Treatment of neonatal seizures.

- **Subset(s) of the paediatric population concerned by the paediatric development**

From birth to less than 28 days

- **Formulation(s)**

Oral suspension (20 mg/ml)
Intravenous formulation to be developed

- **Studies**

Area	Number of studies	Description
Quality	2	Development of oral suspension. Development of an intravenous formulation.
Non-clinical	4	2- week dose range-finding toxicity study in juvenile rats. 39-day juvenile rat toxicity study. 2-week dose range-finding toxicity study in juvenile dogs. 20-day pharmacokinetic study in nursing rat pups.
Clinical	2	Open-label, multiple-dose, study to evaluate pharmacokinetics, safety, and tolerability of carisbamate as adjunctive therapy in neonates with seizures, aged birth to less than 28 days, followed by an open-label extension study (15 months). Open-label, multiple-dose, study to evaluate the pharmacokinetics, safety, and tolerability of intravenously administered carisbamate as adjunctive therapy in neonates with seizures, aged birth less than 28 days, with open-label extension (15 months).

C.3 Condition(s) to be investigated

- Infantile spasms (West Syndrome)
- Lennox-Gastaut Syndrome
- Other paediatric epilepsy syndromes such as Dravet Syndrome, myoclonic astatic syndrome, epilepsy with continuous sharp-waves in sleep, idiopathic partial epilepsy, absence epilepsy.

- **Proposed PIP indication**

Treatment of paediatric patients with Infantile spasms (West Syndrome), Lennox-Gastaut Syndrome and other paediatric epilepsy syndromes such as Dravet Syndrome, myoclonic astatic syndrome, epilepsy with continuous sharp-waves in sleep, idiopathic partial epilepsy, absence epilepsy.

- **Subset(s) of the paediatric population concerned by the paediatric development**

From 1 month to less than 16 years.

- **Formulation(s)**

Film-coated tablets (100 mg, 200 mg, 400 mg)
Oral suspension (20mg/ml)

- **Studies**

Area	Number of studies	Description
Quality	2	Development of paediatric age-appropriate strengths of film-coated tablets. Development of an oral suspension.
Non-clinical	5	2- week dose range-finding toxicity study in juvenile rats. 39-day juvenile rat toxicity study. 2-week dose range-finding toxicity study in juvenile dogs. 20-day pharmacokinetic study in nursing rat pups. Single-dose nonclinical study on the efficacy of carisbamate in a mouse model of Severe Myoclonic Epilepsy in Infancy (SMEI).
Clinical	2	Observational open label (arm 1) placebo controlled, cross-over design (arm 2 and 3) study to evaluate efficacy, safety and tolerability of carisbamate as adjunctive therapy in patients aged 1 month to less than 18 years with infantile spasms (arm 1), Lennox-Gastaut Syndrome (arm 2) and other epileptic syndromes such as Dravet Syndrome, myoclonic astatic syndrome, epilepsy with continuous sharp-waves in sleep, idiopathic partial epilepsy, absence epilepsy (arm 3) followed by an open extension phase (15 months). Randomized, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy, safety, and tolerability of carisbamate (oral suspension and tablets) as ddjunctive therapy in patients aged 1 month to 18 years with a paediatric epileptic syndrome based on the results of the observational study with open label extension (minimum of 15 months).

Measures to address long term follow-up of potential safety issues in relation to paediatric use:	**Yes**
Date of completion of the paediatric investigation plan:	**By October 2017**
Deferral for some or all studies contained in the paediatric investigation plan:	**Yes**