Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

(Zopiclone)

ZIMOVANE, ZIMOVANE LS

UK/W/068/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	21 November 2014

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Zimovane, Zimovane LS Imovane , Limovan , Ximovan, Datolan, Siaten
INN (or common name) of the active substance(s):	Zopiclone
MAH (s):	Sanofi-aventis
Pharmaco-therapeutic group (ATC Code):	N05CF01 - Benzodiazepine related drugs
Pharmaceutical form(s) and strength(s):	3.75mg film-coated tablets 5 mg film-coated tablets 7.5mg film-coated tablets

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.1, 4.2 and 4.4.

Summary of outcome

☒ Paediatric information clarified: 4.1, 4.2 and 4.4

II. RECOMMENDATION

A Type IB variation to be requested from the MAH by 06 February 2015.

The following text should be included in the relevant SmPC and PL sections:

- Section 4.1 Therapeutic indications:

  Addition of the wording *'in adults'*.

- Sections 4.2 Posology and method of administration and 4.4 Special warnings and special precautions for use

  Addition of the following text*: Paediatric population: Zopiclone should not be used children and adolescents less than 18 years. The safety and efficacy of zopiclone in children and adolescents aged less than 18 years have not been established.*

III. INTRODUCTION

Sanofi-Aventis submitted a short critical expert overview for zopiclone, in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The submission included safety data only. These were derived from a review of the MAH's pharmacovigilance database and included one serious adverse event from a local postmarketing surveillance study.

The MAH stated that the submitted data do not influence the benefit risk for zopiclone and that there was no consequential regulatory action.

The initial review of the data identified missing information, inconsistencies and inadequate detail in the provided data. This precluded reaching a final conclusion at this stage.

The MAH was asked to provide the following:

1) Information regarding trial RP27267/ZD 5001-NZL-N/A-NZ.

2) CIOMs report forms for the fatal cases and for those cases with reactions that are not listed in the SmPC such as growth retardation, libido increased, coagulopathy, convulsion.

3) Clarifications on the inconsistencies with regard to case numbers and percentage of cases in individual age groups as outlined in this report.

4) Clarification of the age ranges used in the safety review, as the age ranges overlap. For instance, a child aged 12 years old could be considered to be in the 'Children' category or in the 'Adolescents' category.

5) A proposal for a harmonised text for the paediatric aspects of the product information. This should take into account the guidance provided in the Guideline On Summary Of Product Characteristics (SmPC) September 2009.

Given that the response for to the above request resulted in the provision of new tables summarising adverse events and cases, this report only covers the newly presented information.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Not applicable.

IV.2 < Non-clinical aspects>

Not applicable.

IV.3 <Clinical aspects>

1. Introduction

The submission included safety data only. These were derived from a review of the MAH's pharmacovigilance database and included safety data from a local postmarketing surveillance study.

The MAH did not submit reports or synopses for any clinical studies as they had not identified any published data pertaining to paediatric pharmacokinetics, pharmacodynamics or efficacy.

2. Clinical study

Trial RP27267/ZD 5001-NZL-N/A-NZ

This was a local Post Marketing Surveillance Study conducted in New Zealand in 1989. No Clinical Study Report is available.

One serious adverse event was reported: an overdose in a 17-year-old girl who took 23 tablets of zopiclone (172.5 mg). Treatment with zopiclone was discontinued and the patient recovered. This case was considered medically significant.

31 patients, all adults (ages 25 to 78 years), reported non-serious adverse events. Five patients experienced more than one adverse event. The most frequent adverse events were dysgueusia (n= 17), somnolence (n= 7) and hangover (n= 6). The other non-serious events reported were: agueusia, depression and dry mouth reported in 2 patients each and abnormal dreams, headache and nausea reported in one patient each.

CIOMS case report for the serious case and the line-listing of non-serious cases were provided.

3. Safety review

The Sanofi global pharmacovigilance database was searched for

- Solicited related (either by the investigator or the company) cases.
- Unsolicited medically-confirmed and nonmedically-confirmed cases reported by healthcare professionals, non-healthcare professionals, via Regulatory Authorities, literature cases.

in patients aged < 18 years and exposed to zopiclone. Cut-off date for the search was 31 March 2013. Cases of drug exposure during pregnancy and/or lactation were not taken into account in the analysis.

The Medical Dictionary for Regulatory Activities (MedDRA), version 15.1, was used for coding the solicited AEs and the unsolicited Adverse Drug Reactions (ADRs).

Zopiclone was considered to be taken in overdose when reported as such or when the daily dose was higher than 7.5 mg (maximum adult daily dose).

Age categories were defined as follows:

- Neonates: 0 to < 28 days or patients reported as neonates,
- Infants: 28 days to < 24 months or patients reported as infants,
- Children: 24 months to <12 years or patients reported as children,
- Adolescents: 12 to < 18 years or patients reported as adolescents.

Solicited cases:

One serious related case was reported in the paediatric population as part of a local Post Marketing Surveillance Study conducted in New Zealand in 1989 (RP27267/ZD 5001-NZL-N/A-NZ.) This case is described above.

Unsolicited cases:

262 unsolicited adverse events for reported for 77 patients/cases (neonates n=4, infants and children n=27, adolescents n=46). 111 adverse events were serious.

Of the 77 individual cases, 36 were classified non-serious and 41 serious.

The 77 cases included 31 cases of overdose (intentional or accidental) and 46 cases of other adverse events. Outcomes for overdose were: recovered n= 24, death n=2, unspecified n = 5.

Fatal cases:

Three fatal cases were reported in the 12 – 18 years age-group. Table 1 provides an overview of these cases.

Table 1: Fatal cases

Case Id Sex/age	Relevant medical history	PT	Outcome	Summary
200022402FR F/13 years	Not reported	Intentional overdose	Fatal	Suicide with intentional overdose of methadone and zopiclone
200420388GDDC F/17 years	None	Completed suicide	Fatal	The patient was found dead at home (suicide note). Concomitant medications included also mirtazapine, diltiazem and paracetamol. Results of autopsy not available.
200513372EU* F/17 years	Not reported	Completed suicide Intentional overdose	Fatal	The patient was found dead at home (suicide note). Concomitant medications included also mirtazapine, diltiazem and paracetamol.

Assessor's comment

Case 200022402FR had a fatal methadone blood level. Case 200420388GDDC had been receiving zopiclone for an unspecified indication/duration/dosage.

Cases 200420388GDDC and 200513372EU* appear very similar. The MAH clarified that both cases were reported by health authorities. Case numbers were different (Great Britain Health Authority Nr: 495762 and 478962), therefore the sources of documents were considered different and these cases were not considered as duplicate cases.

The reported fatal cases are in the setting of intentional overdose with other CNS-active drugs. The SmPC provides adequate information regarding the manifestations and treatment of overdose.

Zopiclone has been licensed in the UK since 1998. The three reported fatal cases over the period of 15 years do not require amendment of the product information.

Unlisted cases:

The MAH provided an overview for those cases reporting reactions not listed in the SmPC, see Table 2. CIOMS report forms were also provided for these cases.

Table 2: Unlisted cases

Case Id Sex/age	Relevant medical history	PT	Outcome	Summary
200020659FR F/4 months	Not reported	Coma Convulsions Overdose	Unknown	Coma, with Glasgow index 5, Bicetre index 9, with ventricular extrasystoles 3 hours after an overdose (7 tablets of zopiclone). Then, convulsions resistant to anti-epileptic treatment occurred.
200212633FR M/15 years	Not reported	Coagulopathy Intentional overdose	Recovering	Intentional overdose of zopiclone (4 tablets) and tianeptine (20 tablets) Coagulopathy was diagnosed: fibrinogen, prothrombin, factor II,VII and X were decreased. No clinical symptoms associated. Corrective treatment if any was not provided.
200413060EU M/15 years	Intensive sport practice (7 hours/day)	Growth retardation	Recovering	Growth curve break after 1 year of zopiclone treatment.
NO01-00029 F/17 years	Not reported	Libido increased Sedation	Unknown	Zopiclone has been added to a drink to make a girl sleepy and less resistant to sexual advance.

Assessor's comment

The individual case reports of unlisted reactions do not require amendment of the product information.

Cases of overdose:

31 cases of overdose (intentional or accidental) were identified. 24 patients recovered and 2 adolescents committed suicide by multiple drug ingestion. The outcome was unspecified in the 5 remaining cases. The symptoms reported depend on the dose taken. In cases of mild severity (n = 22), the patients developed somnolence, confusion, dizziness. In more severe cases, the patients may present ataxia, gait disturbances, depressed level of consciousness and coma (n = 9).

The distribution of cases by PTs among the age group is presented in the table below.

Table 3: Distribution of overdose (intentional or accidental) cases by age category

	28 days to < 24 months (n = 4)	**24 months to < 12 yrs (n = 27)**	**12 to <18 years (n = 46)**	**Total of cases (n = 77)**
Accidental overdose	0	9	1	10
Intentional overdose	0	4	12	16
Overdose NOS	1	1	3	5
Total	1	14	16	31

Table 4 provides a summary of cases in a context of overdose, reported PTs associated and outcome by age class.

Assessor's comment

The information provided by the applicant in this section identifies two fatal cases of overdose, whilst the review of fatal cases above identified three such cases. It would appear that case 200420388GDDC has been excluded from the overdose section because 'overdose' was not a reported term in this case. Post-mortem investigations for this case identified 'a trace' of zopiclone.

The great majority of the reported overdose cases in adolescents were of intentional overdose. The reported fatal cases are in the setting of intentional overdose with other CNS-active drugs.

The majority of reported overdose cases in children were accidental ingestion.

Zopiclone is not licensed for use in the paediatric population. The product information should contain the following statement in sections 4.2 and 4.4: 'Zopiclone should not be used children and adolescents less than 18 years.'

The SmPC provides adequate information regarding the manifestations and treatment of overdose.

Table 4 - Summary of unsolicited cases in a context of overdose, reported PTs associated and outcome by age class

Age class	Case Id Sex/Age	PT overdose	Zopiclone dose taken	Short summary	PT associated	Outcome
28 Days - 24 Months	200020659FR F/4 months	Overdose	52,5 mg	The mother gave 7 tablets of zopiclone leading to coma and convulsions. EEG secondarily showed depressed lines. Blood zopiclone level not available. Corrective treatment included antiepileptics.	Coma Convulsions	Unknown
[24 Months-12 years[	200022902FR F/3 years	Accidental overdose	7.5 mg	Dizziness after accidental exposure	Dizziness	Recovered
	200313811FR F/4 years	Intentional overdose	8.5 mg	A depressive mother intentionnally gave an overdose of zopiclone (about 8,5 mg) to her daughter leading to paradoxical reaction. Blood zopiclone level not available. No corrective treatment.	Paradoxical drug reaction Agitation	Recovered
	200313813FR M/4 years	Intentional overdose	12 mg	A depressive mother intentionnally gave an overdose of zopiclone (about 12 mg) to her boy leading to paradoxical reaction. Blood zopiclone level was not available. No corrective treatment.	Paradoxical drug reaction Agitation	Recovered
	200410477FR F/3 years	Accidental overdose	Exact dose unknown (15 to 22.5 mg)	Accidental intake of zopiclone and paroxetine (exact dose was unknown, around 2 at 3 tablets). Corrective treatment: activated charcoal.	Somnolence Gait disturbance	Recovered
	200412684DE M/2,7 years	Accidental overdose	7.5 mg	Ingestion of 1 tablet of zopiclone 7.5mg by accident. Somnolence. No corrective treatment.	Somnolence	Recovered
	200511848FR F/2,5 years	Accidental overdose	Unknown	Accidental drugs poly-intoxication (cyamemazine, paracetamol + dextropropoxyphene, oxazepam, mianserin, clomipramine, zopiclone and propanolol. Miosis, somnolence and agitation. Blood toxic check-up positive for benzodiazepines and urine check-up positive for phenothiazines and benzodiazepines. No corrective treatment if any was provided.	Miosis Somnolence	Recovered
	200612956JP M/10 years	Accidental overdose	Unknown	No information available	Dizziness	Recovered
	2010SA066842 M/7 years	Accidental overdose	7.5 mg	Medication error: ingestion of one tablet of zopiclone instead of amoxicillin. Ataxia and somnolence. No corrective treatment.	Wrong drug administered Somnolence Ataxia	Recovered

Age class	Case Id Sex/Age	PT overdose	Zopiclone dose taken	Short summary	PT associated	Outcome
	2011SA032286 M/11 years	Intentional overdose	Exact dose unknown (105 to 120 mg)	Intentional ingestion of between 14 and 16 tablets of zopiclone leading to irritability. Corrective treatment: gastric lavage and flumazenil	Irritability	Recovered
	DE01-03161 M/3 years	Accidental overdose	3.75 mg	Accidental ingestion of 1/2 tablet.	Paradoxical reaction Visual hallucinations	Recovered
	DE01-03458 M/6 years	Accidental overdose	22.5 mg	Accidental ingestion of 3 tablets leading to dysarthria and balance disorder. Corrective treatment: activated carbon and sodium sulphate	Dysarthria Balance disorder	Recovered
	FR01-04406 F/3 years	Accidental overdose	7.5 mg	No information available	Ataxia	Recovered
	FR01-08846 F/11 years	Intentional overdose	45 mg	Intentional ingestion of 6 tablets of zopiclone by an 11-year-old child. Somnolence. Corrective treatment: gastric lavage and activated charcoal	Somnolence	Recovered
	FR01-10178 F/2 years	Overdose	3,75 mg	Ingestion of 1/2 tablet. No corrective treatment.	Sedation	Recovered
[12 – 18 years[	200022402FR F/13 years	Intentional overdose	Unknown	Intentional overdose of methadone (60 mg) and zopiclone (dose NOS) by a 13-year-old child leading to death. Post-mortem blood dosage showed a level of methadone of 600 ng/ml (letal) and a level of 780 ng/ml of zopiclone.	No ADR	Fatal
	200212633FR M/15 years	Intentional overdose	30 mg	Intentional overdose of zopiclone (4 tablets) and tianeptine (20 tablets) by a 15-year-old adolescent. Medical history was unknown. Coagulopathy was diagnosed: fibrinogen, prothrombin, factor II,VII and X were decreased. No clinical symptoms associated. Corrective treatment if any was not provided	Coagulopathy	Recovering
	200312284FR F/14 years	Intentional overdose	15 mg	Intentional overdose of bromazepam (1 tablet), zolpidem (4 tablets), zopiclone (2 tablets) and paracetamol (2 tablets) leading to somnolence by a 14-year-old adolescent. No corrective treatment provided.	Somnolence	Recovered
	200512048JP M/17 years	Overdose	75 mg	Somnolence after ingestion of 10 tablets of zopiclone. Cirumstances of the overdose were not specified. Corrective treatment if any was not provided.	Somnolence	Unknown

Age class	Case Id Sex/Age	PT overdose	Zopiclone dose taken	Short summary	PT associated	Outcome
	200513372EU F/17 years	Intentional overdose	Unknown	A 17-year-old female patient committed suicide. Post-mortem femoral blood samples showed significant concentrations of mirtazapine and evidence of diltiazem, paracetamol and zopiclone. Post mortem blood concentrations (mg/L): Mirtazapine 4.4 Normirtazapine 0.7 Diltiazem 4.2 Paracetamol 70. Zopiclone trace.	Completed suicide	Fatal
	2010SA003757 F/15 years	Intentional overdose	15 mg	A 15-year-old female patient intentionally took once 2 tablets of zopiclone of 7.5 mg and 3 tablets of mirtazapine of 30 mg and experienced: weakness, metallic taste, psychomotor retardation, blurred speech and visual disturbances. Benzodiazepine in serum and urine not detectable. Mirtazapine and metablolites positive in urine.	Speech disorder Visual impairment Asthenia Dysgeusia Psychomotor retardation	Recovered
	2012SA028926 F/14 years	Intentional overdose	45 mg	A 14-year-old female patient intentionally took 6 tablets of zopiclone tablet and experienced somnolence. Corrective treatment if any was not provided	Somnolence	Recovered
	2013SA007733 F/15 years	Intentional overdose	75 mg	A 15-year-old female patient took intentional overdose with 10 tablets of zopiclone 7.5 mg and presented with vertigo, nausea, mild asthenia and amnesia. The search of benzodiazepine, barbiturate and phenothiazine in the urines was negative. No corrective treatment was reported.	Nausea Asthenia Amnesia Vertigo	Recovered
	DE01-03052 F/16 years	Intentional overdose	75 mg	No information available	Depressive mood	Unknown
	DE01-03424 F/16 years	Intentional overdose	150 mg	A 16-year-old female patient intentionally took once 20 tablets of zopiclone, amoxicillin and dimenhydrinate. Corrective treatment included ipecacuanh.	Suicide attempt	Recovered
	DE01-03425 F/14 years	Intentional overdose	150 mg	A 14-year-old female patient intentionally took once 20 tablets of zopiclone, amoxicillin and dimenhydrinate. Corrective treatment included ipecacuanh.	Suicide attempt	Recovered
	FR01-05503 F/ 14 years	Overdose	135 mg	A 14-year-old female patient intentionally took 18 tablets of zopiclone tablet and experienced confusion, dysarthria and drowsiness. Corrective treatment included gastric lavage.	Suicide attempt Confusional state Amnesia	Recovered
	FR01-08842 F/ 17 years	Intentional overdose	150 mg	A 17-year-old female patient intentionally took 20 tablets of zopiclone tablet and experienced somnolence. Corrective treatment if any was not provided.	Somnolence	Recovered
	IT01-00789 M/16 years	Overdose	75 mg	A 16-year-old male patient intentionally took once 10 tablets of zopiclone and developed confusion and somnolence. Corrective treatment included gastric lavage, activated charcoal and furosemide.	Confusional state Somnolence	Unknown

Age class	Case Id Sex/Age	PT overdose	Zopiclone dose taken	Short summary	PT associated	Outcome
	JP01-01056 F/15 years	Intentional overdose	112.5 mg	A 15-year-old female patient intentionally took once 15 tablets of zopiclone and developed dizziness, amnesia and somnolence. Corrective treatment if any was not provided.	Amnesia Somnolence Dizziness	Recovered
	JP01-01143 F/13 years	Accidental overdose	100 mg	A 13-year-old female patient intentionally took once 10 tablets of zopiclone and developed amnesia and consciousness decreased. Corrective treatment if any was not provided.	Depressed level of consciousness Amnesia	Unknown

Assessor's comment

Table 4 lists 'suicide attempt' as preferred term (PT) for three adolescents. Table 5 lists five suicide attempts, whilst Table 6 lists three suicide attempts. The MAH has not provided an explanation of this discrepancy.

All unsolicited adverse events and cases by SOC, preferred term and seriousness

The following tables provide an overview of all reported adverse events and cases by SOC, preferred term and seriousness (Table 5) and information on the distribution in the 3 most involved SOCs of unsolicited cases and among age-groups (Table 6).

Table 5 Unsolicited adverse events and cases by SOC, PT and event seriousness

		Non-serious	Serious	Unknown	**Total**
Blood and lymphatic system disorders	Coagulopathy	-	1	-	**1**
	Thrombocytopenia	1	-	-	**1**
Blood and lymphatic system disorders	**cases**	**1**	**1**	**-**	**2**
Blood and lymphatic system disorders	**reactions**	**1**	**1**	**-**	**2**
Ear and labyrinth disorders	Vertigo	-	1	-	**1**
Ear and labyrinth disorders	**cases**	**-**	**1**	**-**	**1**
Ear and labyrinth disorders	**reactions**	**-**	**1**	**-**	**1**
Eye disorders	Dry eye	2	-	-	**2**
	Miosis	-	1	-	**1**
	Visual impairment	1	1	-	**2**
Eye disorders	**cases**	**2**	**2**	**-**	**4**
Eye disorders	**reactions**	**3**	**2**	**-**	**5**
Gastrointestinal disorders	Dry mouth	1	-	-	**1**
	Nausea	1	1	-	**2**
	Salivary hypersecretion	1	-	-	**1**
	Vomiting	2	-	-	**2**
Gastrointestinal disorders	**cases**	**4**	**1**	**-**	**5**
Gastrointestinal disorders	**reactions**	**5**	**1**	**-**	**6**
General disorders and administration site conditions	Abasia	1	-	-	**1**
	Asthenia	1	2	-	**3**
	Condition aggravated	-	-	2	**2**
	Crying	-	-	1	**1**
	Drug interaction	-	-	1	**1**
	Feeling abnormal	1	-	-	**1**
	Gait disturbance	-	3	-	**3**
	Malaise	1	-	-	**1**
	Paradoxical drug reaction	-	2	-	**2**
	Product taste abnormal	1	-	-	**1**
General disorders and administration site conditions	**cases**	**4**	**6**	**3**	**13**
General disorders and administration site conditions	**reactions**	**5**	**7**	**4**	**16**
Immune system disorders	Anaphylactic reaction	-	1	-	**1**
Immune system disorders	**cases**	**-**	**1**	**-**	**1**
Immune system disorders	**reactions**	**-**	**1**	**-**	**1**

		Non-serious	Serious	Unknown	**Total**
Injury, poisoning and procedural complications	Accidental exposure to product	6	-	-	**6**
	Accidental exposure to product by child	1	2	1	**4**
	Accidental overdose	2	7	7	**16**
	Fall	1	-	-	**1**
	Intentional overdose	2	13	7	**22**
	Medication error	-	-	25	**25**
	Overdose	2	5	11	**18**
	Toxicity to various agents	-	2	-	**2**
	Wrong drug administered	-	1	-	**1**
Injury, poisoning and procedural complications	**cases**	**11**	**20**	**37**	**51**
Injury, poisoning and procedural complications	**reactions**	**14**	**30**	**51**	**95**
Metabolism and nutrition disorders	Hypoglycaemia	2	-	-	**2**
Metabolism and nutrition disorders	**cases**	**1**	**-**	**-**	**1**
Metabolism and nutrition disorders	**reactions**	**2**	**-**	**-**	**2**
Musculoskeletal and connective tissue disorders	Growth retardation	1	-	-	**1**
	Muscular weakness	1	-	-	**1**
Musculoskeletal and connective tissue disorders	**cases**	**2**	**-**	**-**	**2**
Musculoskeletal and connective tissue disorders	**reactions**	**2**	**-**	**-**	**2**
Nervous system disorders	Akathisia	1	-	-	**1**
	Altered state of consciousness	-	1	-	**1**
	Amnesia	7	3	-	**10**
	Ataxia	1	3	-	**4**
	Balance disorder	-	2	-	**2**
	Coma	-	1	-	**1**
	Convulsion	-	1	-	**1**
	Depressed level of consciousness	2	3	-	**5**
	Dizziness	7	1	-	**8**
	Dysarthria	-	2	-	**2**
	Dysgeusia	1	1	-	**2**
	Dyskinesia	2	-	-	**2**
	Grand mal convulsion	-	1	-	**1**
	Headache	3	-	-	**3**
	Loss of consciousness	-	1	-	**1**
	Sedation	4	2	-	**6**
	Somnolence	5	12	-	**17**
	Speech disorder	-	1	-	**1**
	Syncope	-	1	-	**1**
	Tremor	1	2	-	**3**
Nervous system disorders	**cases**	**17**	**21**	**-**	**38**

		Non-serious	Serious	Unknown	Total
Nervous system disorders	**reactions**	**34**	**38**	**-**	**72**
Psychiatric disorders	Abnormal behaviour	3	3	-	**6**
	Aggression	-	2	-	**2**
	Agitation	4	1	2	**7**
	Anxiety	1	-	-	**1**
	Bradyphrenia	-	-	1	**1**
	Completed suicide	-	2	-	**2**
	Confusional state	1	5	-	**6**
	Delusion	2	-	-	**2**
	Drug abuse	4	2	-	**6**
	Hallucination	4	3	-	**7**
	Hallucination, visual	-	1	-	**1**
	Irritability	1	2	-	**3**
	Libido increased	2	-	-	**2**
	Moaning	1	-	-	**1**
	Psychomotor retardation	-	1	-	**1**
	Somnambulism	1	-	-	**1**
	Suicide attempt	-	5	-	**5**
	Withdrawal syndrome	1	-	-	**1**
Psychiatric disorders	**cases**	**11**	**14**	**3**	**28**
Psychiatric disorders	**reactions**	**25**	**27**	**3**	**55**
Skin and subcutaneous tissue disorders	Urticaria	-	2	-	**2**
Skin and subcutaneous tissue disorders	**cases**	**-**	**1**	**-**	**1**
Skin and subcutaneous tissue disorders	**reactions**	**-**	**2**	**-**	**2**
Surgical and medical procedures	Intentional drug misuse	2	-	-	**2**
Surgical and medical procedures	**cases**	**2**	**-**	**-**	**2**
Surgical and medical procedures	**reactions**	**2**	**-**	**-**	**2**
Vascular disorders	Circulatory collapse	-	1	-	**1**
Vascular disorders	**cases**	**-**	**1**	**-**	**1**
Vascular disorders	**reactions**	**-**	**1**	**-**	**1**
Total reactions		**93**	**111**	**58**	**262**
Total cases		**38**	**41**	**41**	**77**

Table 6: Distribution of PTs in the 3 most involved SOCs of unsolicited cases and among age-groups.

SOC	PT	28 days to < 24 months (n = 4)	24 months to <12 years (n = 27)	12 to <18 years (n = 46)
Injury, poisoning and procedural complications	Accidental drug intake by child		4	
	Accidental exposure to product	2	4	
	Accidental overdose		9	1
	Fall			1
	Intentional overdose		4	12
	Medication error	3	10	3
	Overdose	1	5	9
	Toxicity to various agents			2
	Wrong drug administered		1	
Injury, poisoning and procedural complications - Cases		**4**	**25**	**22**
Injury, poisoning and procedural complications - Reactions		**6**	**53**	**36**
Psychiatric disorders	Abnormal behaviour		1	3
	Aggression			2
	Agitation		4	2
	Anxiety			1
	Bradyphrenia			1
	Completed suicide			2
	Confusional state			4
	Delusion			1
	Drug abuse			3
	Hallucination		2	2
	Hallucination, visual		1	
	Intentional drug misuse		2	
	Libido increased			1
	Moaning			1
	Psychomotor retardation			1
	Somnambulism			1
	Suicide attempt			3
	Withdrawal syndrome			1
Psychiatric disorders - Cases			**7**	**21**
Psychiatric disorders - Reactions			**12**	**42**
Nervous system disorders	Akathisia			1
	Altered state of consciousness			1
	Amnesia			6
	Ataxia		3	
	Balance disorder		1	
	Coma	1		
	Convulsion	1		

SOC	PT	28 days to < 24 months (n = 4)	24 months to <12 years (n = 27)	12 to <18 years (n = 46)
	Depressed level of consciousness	1	1	1
	Dizziness		3	3
	Dysarthria		1	
	Dysgeusia			2
	Dyskinesia			1
	Grand mal convulsion			1
	Headache			2
	Loss of consciousness			1
	Sedation	1	1	1
	Somnolence		6	7
	Speech disorder			1
	Syncope			1
	Tremor			2
Nervous system disorders - Cases		**2**	**12**	**24**
Nervous system disorders - Reactions		**6**	**21**	**45**

3. Discussion on clinical aspects and conclusion

The MAH provided a review of their safety database with respect to paediatric adverse event reports for zopiclone.

The majority of reports concern cases of overdose and cases in the nervous system disorders and psychiatric disorders SOC. The reported adverse events are generally in line with the known safety profile of the drug. Individual cases of unlisted reactions have been reported. These cases provide inadequate evidence to justify reflection in the product information. The SmPC provides adequate information regarding the manifestations and treatment of overdose.

Zopiclone is not licensed for use in the paediatric population. It is recommended that the product information be amended to clearly state that zopiclone should not be used children and adolescents less than 18 years.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

The MAH provided a review of their safety database with respect to paediatric adverse event reports for zopiclone.

The majority of reports concern cases of overdose and cases in the nervous system disorders and psychiatric disorders SOC. The reported adverse events are generally in line with the known safety profile of the drug. Individual cases of unlisted reactions have been reported; these cases provide inadequate evidence to justify reflection in the product information. The SmPC provides adequate information regarding the manifestations and treatment of overdose.

Zopiclone is not licensed for use in the paediatric population. The product information be amended to clearly state this fact.

➢ Recommendation

A Type IB variation to be requested from the MAH by 06 February 2015.

The following text is proposed for inclusion in the relevant SmPC and PL sections:

- Section 4.1 Therapeutic indications:

  Addition of the wording *'in adults'*.

- Sections 4.2 Posology and method of administration and 4.4 Special warnings and special precautions for use

  Addition of the following text*: Paediatric population: Zopiclone should not be used children and adolescents less than 18 years. The safety and efficacy of zopiclone in children and adolescents aged less than 18 years have not been established.*

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Country	MAH	Name of the medicinal product	Strength(s)	Pharmaceutical form	Active Substance(s)
Denmark	SANOFI-AVENTIS DENMARK A/S	IMOVANE	7.5 mg	Film-coated tablet	Zopiclone
Estonia	SANOFI-AVENTIS ESTONIA OÜ	IMOVANE, 7,5 MG OHUKESE POLUMEERIKATTEGA TABLETID	7.5 mg	Film-coated tablet	Zopiclone
Finland	SANOFI OY	IMOVANE 5 MG TABLETTI, KALVOPAALLYSTEINEN	5 mg	Film-coated tablet	Zopiclone
Finland	SANOFI OY	IMOVANE 7,5 MG TABLETTI, KALVOPAALLYSTEINEN	7.5 mg	Film-coated tablet	Zopiclone
France	SANOFI-AVENTIS FRANCE	IMOVANE 3,75 MG, COMPRIME PELLICULE	3.75 mg	Film-coated tablet	Zopiclone
France	SANOFI-AVENTIS FRANCE	IMOVANE 7,5 MG, COMPRIMÉ PELLICULÉ SÉCABLE	7.5 mg	Film-coated tablet	Zopiclone
Germany	SANOFI-AVENTIS DEUTSCHLAND GMBH	XIMOVAN	7.5 mg	Film-coated tablet	Zopiclone
Hungary	SANOFI-AVENTIS PRIVATE CO LTD	IMOVANE 7,5 MG FILMTABLETTA	7.5 mg	Film-coated tablet	Zopiclone
Iceland	SANOFI-AVENTIS NORGE AS	IMOVANE 5 MG FILM-COATED TABLETS	5 mg	Film-coated tablet	Zopiclone
Iceland	SANOFI-AVENTIS NORGE AS	IMOVANE 7,5 MG FILM-COATED TABLETS	7.5 mg	Film-coated tablet	Zopiclone
Italy	SANOFI SPA	IMOVANE	7.5 mg	Film-coated tablet	Zopiclone
Latvia	SANOFI-AVENTIS LATVIA SIA	IMOVANE 7,5 MG FILM-COATED TABLETS	7.5 mg	Film-coated tablet	Zopiclone
Lithuania	UAB SANOFI-AVENTIS LIETUVA	IMOVANE 7,5 MG FILM-COATED TABLETS	7.5 mg	Film-coated tablet	Zopiclone
Netherlands	SANOFI-AVENTIS NETHERLANDS B.V.	IMOVANE	7.5 mg	Film-coated tablet	Zopiclone

Norway	SANOFI-AVENTIS NORGE AS	IMOVANE	5 mg	Film-coated tablet	Zopiclone
Norway	SANOFI-AVENTIS NORGE AS	IMOVANE	7.5 mg	Film-coated tablet	Zopiclone
Poland	SANOFI-AVENTIS FRANCE	IMOVANE	7.5 mg	Coated tablet	Zopiclone
Romania	SANOFI-AVENTIS FRANCE	IMOVANE 7,5 MG	7.5 mg	Film-coated tablet	Zopiclone
Spain	ITALFARMACO	SIATEN	7.5 mg	Film-coated tablet	Zopiclone
Spain	SANOFI-AVENTIS SA	LIMOVAN 7,5 MG COMPRIMIDOS RECUBIERTOS CON PELICULA	7.5 mg	Film-coated tablet	Zopiclone
Spain	FAES LABORATORIOS	DATOLAN COMP. 7,5 MG	7.5 mg	Film-coated tablet	Zopiclone
United-Kingdom	AVENTIS PHARMA LTD UK	ZIMOVANE LS 3.75MG FILM-COATED TABLETS	3.75 mg	Film-coated tablet	Zopiclone
United-Kingdom	AVENTIS PHARMA LTD UK	ZIMOVANE 7.5 MG FILM-COATED TABLETS	7.5 mg	Film-coated tablet	Zopiclone