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

(Tramadol)

Zydol

IE/W/0016/pdWS/001

Rapporteur:	Ireland
Finalisation procedure (day 120):	01/06/2016

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Zydol
INN (or common name) of the active substance(s):	Tramadol Hydrochloride
MAH (s):	See section X
Pharmacotherapeutic group (ATC Code):	N02AX02
Pharmaceutical form(s) and strength(s):	50mg Capsule Hard 120 mg/2ml Solution for Injection 100 mg prolonged release tablet 150 mg prolonged release tablet 200 mg prolonged release tablet 50mg dispersible tablet 100mg/mL oral solution 100mg suppositories

I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 5.1 and 5.2.
No PL changes are proposed.

Summary of outcome

☐ No change

☒ Change to SmPC, editorial and harmonising changes to section 4.2, section 5.1 to include a summary of paediatric clinical trials data, and to section 5.2 to include neonatal and infant PK data.

☐ New study data

☐ New safety information

☒ Paediatric information clarified – as above

☐ New indication

II. RECOMMENDATION

Following the assessment of the data presented by the applicant, the RMS has concluded that there is merit in including a brief summary of the paediatric clinical trials data in section 5.1, and to include PK data for paediatric subjects below the age of 1 year in section 5.2. However, the data presented are not sufficient to suggest an n extension of the indication to include these patients, and as such no change to section 4.1 is proposed. The proposal of the applicant to harmonise section 4.2 with respect to age limits is endorsed.

A minor editorial change to section 4.2, cross-referencing the proposed change to section 5.1 is also recommended.

III. INTRODUCTION

Several MAHs submitted several completed paediatric studies for tramadol, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for tramadol and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

The I.V. oral solid and oral liquid formulations were used in the clinical trials submitted by the applicant. Routes of administration used in the various clinical trials included oral, intravenous, rectal, subcutaneous infiltration and caudal.

IV.2 Non-clinical aspects

No non-clinical studies were submitted as part of this procedure, and so this section is not applicable

IV.3 Clinical aspects

1. Introduction

The MAH submitted reports and extended synopses for the following pharmacokinetic studies:

Table 1: Clinical trials that gathered pharmacokinetic results from pediatric subjects

Source	Age	Tramadol HCl dose and route of administration	Number of subjects	Regimen, duration	Sampling scheme
Company-sponsored trials					
FO-PK401	2.2y-5y 1.2y-2.8y	2 mg/kg i.v. 2 mg/kg caudal	10 10	Single dose	extensive
FE-PK426	1.2y-6.6y 5.5y-12y	2 mg/kg i.v. 2 mg/kg caudal	12 5	Single dose	extensive
WIS-AL-TRA-PCP1	2y-8y	1-2 mg/kg i.v.	104	Single dose	sparse
TRAM-PEDS-001/ TRAM-PEDS-006	7y-16y	1-2 mg/kg p.o.	38	Single dose	medium
TRAM-PEDS-007	8y-15y	1-2 mg/kg p.o.	17 [a]	4 times daily (every 6 h), 3 days	medium
Trials in the public domain					
Claahsen-van der Grinten et al. (2005)	Neonates	Administration to mothers giving birth: 100-200 mg i.m. (blood sample from mother, umbilical cord and child)	22 [a]	Single dose	sparse
Allegaert et al.2005a	Neonates	Loading dose 2 mg/kg i.v. plus continuous infusion 5 mg/kg for 24 h	20 [a]	Loading dose plus continuous infusion 24 h	extensive
Allegaert et al. 2005b	Neonates	Loading dose 2 mg/kg i.v. plus continuous infusion 5 mg/kg for 24 h	20 [a]	Loading dose plus continuous infusion 24 h	extensive
Allegaert et al. 2006a	Neonates	Loading dose 2 mg/kg i.v. plus continuous infusion 5 mg/kg for 24 h	25 [a]	Loading dose plus continuous infusion 24 h	urine sampling only
Allegaert et al. 2006b	Neonates	Loading dose 2 mg/kg plus continuous infusion 5 mg/kg for 24 h	25	Loading dose plus continuous infusion 24 h	urine sampling only
Allegaert et al. 2008a Population PK analysis	Neonates	Loading dose 2–3 mg/kg i.v. over >30 min plus continuous infusion 5-8 mg/kg for 24 h	57	Loading dose plus continuous infusion 24 h	urine sampling only
Allegaert et al. 2008b	Neonates	Loading dose of 2 mg/kg i.v. over 30 min plus continuous infusion 5–8 mg/kg for 24 h	59	Loading dose plus continuous infusion 24 h	urine sampling only

Allegaert et al. 2008c	Neonates	Loading dose of 2 mg/kg i.v. over 30 min plus continuous infusion 5–8 mg/kg for 24 h	86 (including 29 reported previously)	Loading dose plus continuous infusion 24 h	urine sampling only
Allegaert et al. 2011 Population PK analysis of previously reported data	Neonates, 1y-8y old subjects, adults	Dose not given	57 neonates, 33 children (1y-8y), 32 adults	Not available	not applicable
Bressolle et al. 2009	1y-8y	Loading dose of 2 mg/kg i.v. over 10 min plus continuous infusion 8 mg/kg for 24 h	25	Loading dose plus continuous infusion 24 h	extensive
Abdel Rahman et al. 2002	7y-16y	Body weight adjusted dose of 50 mg tablets	26 [b]	Single dose	medium
Vandenbossche et al. 2015 Population PK analysis of previously reported data	7y-16y	Single oral dose of 25-100 mg; multiple oral doses of tablets every 6 hours for 3 days	59	Single dose Multiple dose	medium

Trial entries in the table were sorted by age of the youngest subject in the trial.

a) Number of subjects available for pharmacokinetics evaluation.

b) Data reported in this publication have been taken from subjects participating in trials TRAM-PEDS-001 and TRAM-PEDS-006.

h = hours, HCl = hydrochloride, i.v. = intravenous, p.o. = oral, PK = pharmacokinetic, y = years.

For the most part, the submitted clinical studies involving subjects above the age of 1 do not contain any additional PK information likely to alter the currently available knowledge on the efficacy and safety of tramadol in this population. As such, these studies will not be considered further in this report.

Clinical studies in neonates and children below 1 year were considered by the RMS to contain information of potential interest. These studies were;

- Allegaert et al. 2005 a & b,
- Allegaert et al. 2006 a & b
- Allegaert et al. 2008 a, b & c
- Allegaert et al. 2011, and
- Claahsen-van der Grinten et al. 2005

Data from these studies suggest that, while the pharmacokinetic profile in infants becomes similar to adults b 1 year of age, renal immaturity in the neonate can lead to decreased renal elimination, which in turn raises the possibility of significant accumulation in this age cohort. The maturation half-life is approximately 12 weeks, so this risk may significantly decrease the risk of accumulation in older infants. There remains, however s significant gap in the characterisation of the PK profile in this age group, so no recommendation can be made regarding the use of the product in children below 1 at this time. Nonetheless, the available PK data in this cohort should be reflected in section 5.1 of the SmPC.

The applicant has also submitted extended synopses of clinical efficacy studies in the currently indicated age groups. For the most part, the submitted studies involve the administration of tramadol via currently authorised routes of administration, and the results of those trials do not materially alter the currently positive benefit-risk profile of the product.

Studies involving 1149 subjects have investigated the effects of tramadol when given via the caudal/epidural route, both alone and in combination with other analgesics. These studies may provide additional, potentially useful data on the efficacy and safety of tramadol via this route, and while the studies appear to be too heterogeneous to allow a systematic review, the data do suggest an analgesic benefit from the use of tramadol both alone and in combination, via this route. As such these data should also be reflected in section 5.1 of the SmPC.

The relevant studies are;

- Gupta et al. 2003 &2009,	}	Significant benefit with tramadol vs. comparator
- Kumar et al. 2005,	}	
- Prakash et al. 2006,	}	
- Prosser et al. 1997,	}	
- Senel et al. 2001	}	
- Kolsi et al. 2012	}	
- Saleh et al. 2008	}	
- Yildiz et al. 2012	}	
- Gunes et al. 2004	}	
- Taheri et al. 2010	}	
- Gunduz et al. 2001 & 2006	}	No difference between the active treatment groups
- Abdallah et al. 2003,	}	
- Demeran et al 2005	}	
- Ozcwngiz et al. 2001	}	
- Batra et al. 1999	}	Different effects depending on timing of intervention

Although the applicant did present data from safety studies, the data presented did not suggest any reason to change the currently positive benefit-risk profile of the product in the licensed age groups. Information from studies conducted in neonates and infants below 1 year did not reveal an adverse event profile significantly different to that associated with use in older children.

Details of all these clinical studies can be found in the Clinical Overview provided by the applicant.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION AT DAY 70

- **Overall conclusion**

While no additional data have been provided which are likely to change the paediatric age groups in which the product is currently recommended for use nor the recommended routes of administration, the data provided do provide information which would be useful to healthcare professionals, and as such should be reflected appropriately in section 5.1 of the SmPC.

- **Preliminary Recommendation**

Based on the data submitted, the MAH should suggest appropriate wording for section 5.1 and 5.2 of the SmPC to reflect the suggestions contained above regarding the PK profile of tramadol in neonates and infants below 1 year, and to reflect the results of studies investigating the administration of tramadol via the caudal/epidural route as part of this work-sharing procedure.

- **Comments from Member States**

Comments were received from CMS-DE and CMS-NL

CMS-DE
We do not see the necessity to include an additional wording for section 5.1/5.2 of the SmPC
1. to reflect the suggestions regarding the PK profile of tramadol in neonates and infants below 1 year, and
2. to reflect the results of studies investigating the administration of tramadol via the caudal/epidural route as part of this work-sharing procedure
since in DE tramadol-containing products are
1. not approved for neonates and infants below 1 year and are also
2. not approved for the caudal/epidural route.

However, the situation may be different in other MSs and probably in some countries additional information in Section 5.1/5.2 may be helpful.

On the other hand, Section 5.1/5.2 of the current Originator's SmPC in DE does not contain any information concerning the paediatric population. So, a prerequisite for including information on neonates and infants below 1 year in Section 5.1/5.2 would be - as a first step - a harmonised wording for Section 5.1/5.2 summarizing the results of all clinically relevant PK, PD and/or efficacy studies conducted in children older than 1 year.

CMS-NL
Please be informed that we endorse the Rapporteur's assessment.
One minor comment: It is kindly noted that the requested update of the paediatric PK data rather belong to SmPC section 5.2, instead of section 5.1.

- **Consolidated Recommendation**

The comments of the CMSs are welcomed. The proposal from DE that the product information in sections 5.1 and 5.2 be harmonised with regards to patients above age 1 is welcome, and the applicant should consider ways to harmonise the wording in those sections, preferably using a work-sharing variation procedure.

In addition, the applicant is requested to propose wording to reflect the PK profile of tramadol in neonates and infants below 1 year, and to reflect the results of studies investigating the administration of tramadol via the caudal/epidural route as part of this work-sharing procedure, as endorsed by CMS-NL.

VI. RESPONSE OF APPLICANT TO CONSOLIDATED QUESTIONS

Question 1:

The comments of the CMSs are welcomed. The proposal from DE that the product information in sections 5.1 and 5.2 be harmonised with regards to patients above age 1 is welcome, and the applicant should consider ways to harmonise the wording in those sections, preferably using a work-sharing variation procedure.

Response:

The applicant generally agrees with the proposal to provide the relevant information on PK and efficacy for tramadol in the paediatric population in the SmPCs sections 5.1 and 5.2. As there are no relevant PD data, such information cannot be included in the respective section.

For clarification purposes, the applicant would like to point out that the information mentioned above is not only missing in the product information registered in CMS-DE, but has so far been absent from the originator's CCDS (Company Core Date sheet) and consequentially from the SmPCs in all concerned member states.

Therefore, the applicant would like to take the opportunity of the current procedure, instead of a subsequent variation procedure, to introduce and agree with EMA/the member states on an appropriate wording for the discussed sections. Such approach is also supported by the applicable CMDh document on Article 45 Worksharing procedure (CMDh/141/2009/Rev2), in which it is stated that an update to the SmPC shall be done in line with the recommendations – thus final outcome - of the Article 45 work-sharing procedure using a Type IB C.1.3a variation procedure. Such procedure type is based on an already agreed wording and no additional supporting data shall be required for submission.

Further, the applicant would like to explain that the proposed text shall be implemented for all products containing tramadol as sole active substance. While the applicant submitted data, for both, tramadol and the combination product tramadol/paracetamol, an inclusion of relevant information into the tramadol/paracetamol SmPCs sections 5.1 and 5.2 is not considered useful at the current stage. This is due to the situation that for paracetamol (which was not developed by the originator of tramadol), up to now no Article 45 Worksharing was performed. Therefore, no consolidated wording for sections 5.1 and 5.2 is available, which could be included in the tramadol/paracetamol product information. This is also mirrored by the fact, that information on Paediatrics in section 5.1 and 5.2 of registered paracetamol SmPCs is sparse and unharmonized. Last, tramadol/paracetamol has received a EMA PIP waiver (decision W/185/2009), therefore only limited clinical data generally exist on the paediatric use of the combination product.

As already indicated in the submitted Critical Expert Overview, the applicant will file variations to harmonize the age limit (thus affecting SmPCs section 4.2) for tramadol and tramadol/paracetamol in those concerned member states that have currently an age limit registered that deviates (in all and overall very few cases, a higher age limit) from the age limits as based on the current scientific knowledge and described in the Critical Expert Overview. As no questions on the age limit were raised in the current procedure, the applicant understands, that the respective age limits, as stated in the Critical Expert Overview and already registered in the high majority of countries, are confirmed.

Please find the proposal for an updated wording on sections 5.1 and 5.2 below:

Section 5.1.:

...

Paediatric population

A total of 651 paediatric subjects in the age range from 1 year to 17 years, including 205 subjects younger than 5 years, were treated with tramadol administered via the enteral or parenteral route and provided efficacy data in clinical trials sponsored by the originators of tramadol. Of these 651 subjects 329 subjects participated in randomized, double-blind trials and 225 subjects in open label uncontrolled trials, the remaining 97 subjects in single-blind or open-label controlled trials.

The indications for pain treatment were pain after (often abdominal) surgery in at least 370 subjects, pain after surgical tooth extractions in 103 subjects, pain due to fractures, burns and other traumas in up to 65 subjects and painful conditions likely to require analgesic treatment for at least 7 days in 113 subjects. At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (or 400 mg per day whatever the lowest) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. An overview of these trials is given in Table 1.

Independent investigators enrolled more than 1400 subjects in the age range from neonate to 17 years into trials with single-dose or multiple-dose tramadol. More than 500 subjects received multiple doses of tramadol, usually in the dosing range from 1 mg/kg to 2 mg/kg. These trials confirmed the efficacy of tramadol without signs that efficacy might diminish over time in this patient population.

Table 1: Randomized, double-blind, observer-blind, or open-label paediatric clinical trials of tramadol performed by originators

Trial ID Indication	Age	Tramadol HCl dose Treatment(s) Route	No. subjects N	 N_T	Analgesic efficacy
Randomized double-blind clinical trials					
078N3-404 Postoperat. pain	1y-10y	(1) Tramadol 0.75-1 mg/kg; maximum 6 doses/24 h; (2) Nalbuphine i.m.	60	30	tramadol = nalbuphine
WIS-AL-TRA-01-27 Postoperat. pain, inguinal surgery	1y-10y	(1) Tramadol 1 mg/kg, 2 mg/kg SD; (2) Pethidine; (3) Placebo i.v.	88	44	tramadol 2 mg/kg > tramadol 1 mg/kg > pethidine > placebo
FO-BM210 Postoperat. pain	2y-7y	Tramadol 1 mg/kg, 2 mg/kg; SD + reinjection if necessary (max. 6 h) i.v.	40	40	tramadol 2 mg/kg > tramadol 1 mg/kg
WIS-AL-TRA-PCP1 Postoperat. pain	2y-8y	(1) Tramadol 1-2 mg/kg SD; (2) Morphine 0.1-0.2 mg/kg i.v.	150	104	tramadol approximately equals morphine
WIS-AL-TRA-02-27 Pain after dental extraction surgery	3y-8y	(1) Tramadol 1.5 mg/kg SD; (2) Placebo oral	60	31	tramadol > placebo
TRAM-PEDS-005 Postoperat. pain	7y-16y	Tramadol 1 mg/kg or 2 mg/kg SD oral	80	80	tramadol 2 mg/kg > tramadol 1 mg/kg
Randomized observer-blinded clinical trial					
TRA-RSA-2 Pain after multiple dental extraction	3y-7y	(1) Tramadol ~2 mg/kg SD; (2) Paracetamol rectal	147	72	tramadol > paracetamol
Open-label, controlled clinical trial					
FO-BM253 Postoperat. pain,	2y-12y	(1) Tramadol 2.0 mg/kg (repeat dosing up to 4 mg/kg);	75	25	tramadol > pethidine > nalbuphine

Trial ID Indication	Age	Tramadol HCl dose Treatment(s) Route	No. subjects N	 N_T	Analgesic efficacy
abdominal surgery		(2) Pethidine; (3) Nalbuphine i.m.			
Open-label, uncontrolled clinical trials					
FO-BM274 Postoperat. pain, fractures, burns, traumas	1y-14y	Tramadol 0.89-2.08 mg/kg; (up to 5 doses, 1 subject with 8 doses) i.v.	65	65	Very good or good analgesia in 83.6%
WIS-AL-TRA86-04-95 Postoperat. pain	5y-12y	Tramadol 2 mg/kg (repeat dosing up to 8 mg/kg per day) i.v. or oral	40	40	Excellent pain relief in 32.5%, very good in 45.0% of subjects
TRAM-PEDS-001 /TRAM-PEDS-006 Postoperat. pain	11y-16y	Tramadol 1-2 mg/kg SD oral	7	7	Mean hourly pain intensity difference -0.7 to -1.1 between 2 h and 8 h
TRAM-PEDS-008 Pain requiring analgesic therapy for at least 7 days	6y-16y	Tramadol 1-2 mg/kg; up to 30 days oral	113	113	Most subjects had their pain reduced at 1 h post dosing

h = hours, HCl = hydrochloride, ID = identification, i.m. = intramuscular, i.v. = intravenous, N = number of paediatric subjects treated and providing efficacy data, N_T = number of paediatric subjects treated with tramadol and providing efficacy data, No. = number, postoperat. = postoperative, SD = single dose, y = year.

The safety profile of tramadol was similar in adult and paediatric patients (aged 1 year to 17 years).

Section 5.2.:
...
Paediatric population
An overview of pharmacokinetic trials in paediatric subjects conducted by the originators of tramadol is provided in Table 2.
The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 7 years to 16 years were found to be similar to those in adults (for examples of terminal elimination half-life in two of the paediatric trials see Table 3 and Table 4).
The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose intravenous administration to subjects aged 1 year to 8 years were generally similar to those of adults when

adjusting for dose by body weight, with a higher between-subject variability in paediatric subjects.
A body weight related dosage is recommended for the administration of tramadol to the age group 1 year to 17 years (see Section 4.2).

Table 2: Clinical trials performed by originators that gathered pharmacokinetic results for tramadol from paediatric subjects

Source	Age	Tramadol HCl dose and route	Number of subjects	Regimen, duration
FO-PK401	2.2y-5y 1.2y-2.8y	2 mg/kg i.v. 2 mg/kg caudal	10 10	Single dose
FE-PK426	1.2y-6.6y 5.5y-12y	2 mg/kg i.v. 2 mg/kg caudal	12 5	Single dose
WIS-AL-TRA-PCP1	2y-8y	1-2 mg/kg i.v.	104	Single dose
TRAM-PEDS-001/ TRAM-PEDS-006	7y-16y	1-2 mg/kg p.o.	38	Single dose
TRAM-PEDS-007	8y-15y	1-2 mg/kg p.o.	17 [a]	4 times daily (every 6 h), 3 days

a) Number of subjects available for pharmacokinetics evaluation.
h = hours, HCl = hydrochloride, i.v. = intravenous, p.o. = oral, y = years.

Table 3: Comparison of single-dose pharmacokinetic parameters of tramadol and O-desmethyltramadol in paediatric subjects (TRAM-PEDS-001/TRAM-PEDS-006) and adults (TRAMAP-PHI-002) after oral administration

Analyte		7y-11y Mean (SD)		12y-16y Mean (SD)		Adult [a] Mean (SD)	
Parameter		Female (N=7)	Male (N=8)	Female (N=9)	Male (N=13)	Female (N = 10)	Male (N = 8)
Tramadol							
$t_{1/2}$	[h]	5.07 (0.71)	4.47 (0.99)	4.87 (0.72)	5.37 (1.31)	5.30 (1.03)	4.92 (0.49)
O-desmethyltramadol							
$t_{1/2}$	[h]	6.45 (1.35)	5.28 (1.50)	5.50 (0.6.0)	7.51 (1.99)	n.a.	n.a.

a) Dose-normalized values.
N = number of subjects, SD = standard deviation, n.a. = not available,
$t_{1/2}$ = terminal elimination half life, y = years.

Table 4: Comparison of pharmacokinetic results for total tramadol and total O-desmethyltramadol after intravenous injection in paediatric subjects (N = 9) (FE-PK426) and 30-minute intravenous infusion in adults (N = 18) (FO-PK395)

Analyte Parameter	FE-PK426 1y-7y Mean ± SD	FO-PK395 Adults Mean ± SD	Mean (FE-PK426) / mean (FO-PK395)
Tramadol			
$t_{1/2}$ [h]	6.40 ± 2.74	5.73 ± 1.11	1.117
O-desmethyltramadol			
$t_{1/2}$ [h]	10.61 ± 8.53	6.65 ± 0.99	1.595
O-desmethyl-tramadol / tramadol ratio [a]	0.18 ± 0.11	0.18 ± 0.07	0.961

Data are adjusted in each case to the same dose of tramadol HCl 2 mg/kg.
Three subjects were excluded from the calculation of means in FO-PK426.
a) The mean O-desmethyltramadol/tramadol serum concentration ratio at the maximum t'_{max} of the mean O-desmethyltramadol serum concentration curve (4 hours post dose) after i.v. injection.
i.v. = intravenous, N = number of subjects, SD = standard deviation,
$t_{1/2}$ = terminal elimination half life.

Question 2:
In addition, the applicant is requested to propose wording to reflect the PK profile of tramadol in neonates and infants below 1 year, and to reflect the results of studies investigating the administration of tramadol via the caudal/epidural route as part of this work-sharing procedure, as endorsed by CMS-NL.

Response:
The applicant agrees to include wording on the PK profile of tramadol in the age range below 1 year and to add relevant information on studies concerning administration via the epidural/caudal route.
The applicant agrees to the comment of CMS-NL, that the latter topic is preferably included into section 5.2 of the CCDS/SmPCs.

Please find the proposal for an updated wording on sections 5.1 and 5.2 below:

Section 5.1.:
...
Paediatric population
... (information as stated under response to Question 1)

Caudal/epidural route of administration

An analgesic benefit was suggested by independent investigators from randomized, controlled, single-dose studies involving more than 600 paediatric subjects (aged 1 year to 14 years) treated with tramadol 1 mg/kg to 2 mg/kg alone or in combination with (levo-) bupivacaine, ketamine, or ropivacaine by caudal/epidural administration.

Section 5.2.:
...
Paediatric population
... (information as stated under response to Question 1)

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates. Adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age. The administration of tramadol to children younger than 1 year is not indicated.

VII. RAPPORTEUR ASSESSMENT OF RESPONSE TO QUESTIONS

Overall, the responses and suggestions of the applicant are acceptable in principle. The proposed text is a little unwieldly, and the addition of the tables impairs the readability of the sections without adding sufficient beneficial information to justify their inclusion.

The RMS proposes a slight alteration to the proposed text, and suggests that this proposal provides sufficient information without undue burden.

Section 5.1
...

Paediatric population

A total of 651 paediatric subjects in the age range from 1 year to 17 years, including 205 subjects younger than 5 years, were treated with tramadol administered via the enteral or parenteral route and provided efficacy data in clinical trials sponsored by the originators of tramadol.
At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine.

Independent investigators enrolled more than 1400 subjects, ranging in age from neonate to 17 years into trials with single-dose or multiple-dose tramadol. More than 500 subjects received multiple doses of tramadol, with doses up to 2 mg/kg. These trials confirmed the efficacy of tramadol without signs that efficacy might diminish over time in this patient population.

The safety profile of tramadol was similar in adult and paediatric patients older than 1 year.

Caudal/epidural route of administration

An analgesic benefit was suggested by independent investigators from randomised, controlled, single-dose studies involving more than 600 paediatric subjects (aged 1 year to 14 years) treated with tramadol 1 mg/kg to 2 mg/kg alone or in combination with (levo-) bupivacaine, ketamine, or ropivacaine by caudal/epidural administration.

Section 5.2
…

Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age. The administration of tramadol to children younger than 1 year is not indicated.

VIII. COMMENTS FROM CMS ON RAPPORTEUR ASSESSMENT

Additional comments were received from CMS-UK and CMS-NL on the preliminary assessment of response.

CMS-NL
The claim regarding the benefits of tramadol as adjuvant analgesic in caudal anaesthesia with local anaesthetics is not supported. As its benefit/risk is uncertain it is proposed to delete corresponding SmPC text.

Rationale:
In the submitted studies by the MAHs, analgesic efficacy of epidural tramadol alone or in combination with anaesthetics was demonstrated in some studies, but not in other studies submitted by the MAHs. Also meta-analyses indicate that the outcomes of trials of tramadol as adjuvant analgesic drug via the caudal route are heterogeneous (Engelman and Marsala. Bayesian enhanced meta-analysis of post –operative analgesic efficacy of additives for caudal analgesia in children. Acta Anaesthesiol Scand 2012; 56:817-832.2012; Stott et al, Efficacy of tramadol with local anaesthetic for caudal analgesia in paediatric surgery: a meta-analysis. European Journal of Anaesthesiology 29:158 June 2012). Clinical relevance of the observed analgesic effect is unclear, since in a comprehensive meta-analysis by Engelman (2012), caudal epidural administration of tramadol was not shown to reduce the number of paediatric patients needing rescue medication. Postoperative nausea and vomiting (PONV) were however about twice as common upon additional caudal epidural tramadol administration as compared to epidural administration of local anaesthetics alone (Engelman 2012, Stott et al. 2012).
Apart from these issues, the MAHs have not demonstrated that physical and chemical properties of registered intravenous tramadol formulations on the European market allow safe off-label epidural administration of tramadol.

Based on above information, there is insufficient evidence to conclude that epidural tramadol treatment is ‘beneficial’ to patients. Because of uncertainties with respect to efficacy as well as potential safety risks associated with caudal epidural tramadol administration, it should not be suggested that caudal epidural tramadol administration is acceptable. Respective text should therefore be removed. If it will be accepted after all, please include information regarding the

uncertainties of efficacy (heterogeneous outcomes, unclear clinical relevance regarding rescue medication) and safety (higher rates of PONV), to inform the prescriber.

CMS-UK
The UK overall supports the conclusions of the rapporteur but would like to raise the following points for consideration by the Rapporteur prior the agreement of the final SmPC text:

1) The wording for 5.1 includes a distinction between the type of studies (innovator and independent) which might be considering confusing in terms of the presentation of the overall paediatric results. The data from studies presented in section 5.1 should be summarised as a whole in a manner that makes it easier for prescribers to understand the impact of these data upon their prescribing.

2) With respect to the data on paediatric epidural use in section 5.1, the wording “An analgesic benefit was suggested” is not consider informative for prescribers during decision making. It is noted that the European Commission’s Guideline on Summary of Product Characteristics (SmPC), September 2009 suggests that brief summary of the design and main endpoints and results should be included in the SmPC to demonstrate the power of the evidence and its applicability in clinical scenarios.

3) The sentence proposed for section 5.2, “The administration of tramadol to children younger than 1 year is not indicated” could be misleading to prescribers. While technically correct, it could be interpreted as a restriction in its licensed indication only to this population, while in fact the use of tramadol is not licensed for any child under the age of 12 years. The UK proposes that this sentence is redundant and should be deleted.

As there is additional wording relevant to paediatric use proposed for sections 5.1 and 5.2, the rapporteur should consider the addition of a sentence of cross reference in section 4.2 to this information, in line with the European Commission’s Guideline on Summary of Product Characteristics (SmPC), September 2009.

Assessor comments:
The comments of both CMS are well taken, and the proposals to amend the product information are for the most part endorsed. However, notwithstanding the recommendations of the SmPC guideline, the rapporteur does not consider the inclusion of study design information to be of benefit in this instance, as it is likely to make the section unwieldly without adding sufficiently useful information. Instead, the SmPC text suggestion of CMS-NL is endorsed, and is repeated below.

IX. RAPPORTEUR’S FINAL OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion
Overall, there are sufficient data to warrant the modification of the product information to include appropriate wording for sections 5.1 and 5.2 of the SmPC regarding, respectively, the results of trials in the paediatric population and the PK profile of tramadol in neonates and infants below 1 year.

Recommendation

The RMS recommends the adoption of the proposed wording changes to sections 5.1 and 5.2 as described. Harmonisation of section 4.2 will be addressed during the forthcoming work-sharing variation.

Section 5.1
...

Paediatric population

Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year (see section 4.2).

Section 5.2
…

Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

X. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance(s) Herbal MPs should be indicated (HERB)*
Laboratorios Gebro Pharma, SA	ES	TIONER CÁPSULAS	50 mg	capsules	Tramadol Hydrochloride
Laboratorios Gebro Pharma, SA	ES	TIONER SOLUCIÓN ORAL	100 mg/ ml	oral drops	Tramadol Hydrochloride
Laboratorios Gebro Pharma, SA	ES	TIONER SOLUCIÓN ORAL	100 mg/ ml	oral drops	Tramadol Hydrochloride
Laboratorios Gebro Pharma, SA	ES	TIONER retard 100 mg comprimidos de liberación prolongada.	100 mg	prolonged-release tablets	Tramadol Hydrochloride
Grünenthal GmbH Germany	RO	Tramal	100 mg	suppositories	Tramadol Hydrochloride
Grünenthal GmbH, Liebermannstrasse A01/501, 2345 Brunn am Gebirge, Austria	AT	Tramal Ampullen Tramal Ampullen	50 mg/ ml 100 mg/ 2ml	solution for injection	Tramadol Hydrochloride
Grünenthal GmbH, Liebermannstrasse A01/501, 2345 Brunn am Gebirge, Austria	AT	Tramal Ampullen Tramal Ampullen	50 mg/ ml 100 mg/ 2ml	solution for injection	Tramadol Hydrochloride

Dott. FORMENTI S.p.A.	IT	Fortradol	100 mg 150mg 200 mg	prolonged release tablets	Tramadol hydrochloride
Ciclum Farma Unipessoal, Lda.	PT	Tramadol Ciclum 100 mg/ml, solução oral	100 mg/ml	Oral drops, solution	Tramadol hydrochloride;
Ciclum Farma Unipessoal, Lda.	PT	Tramadol Ciclum 50 mg, cápsulas	50 mg	Capsule, hard	Tramadol hydrochloride;
SANOFI-AVENTIS FRANCE	FR	TOPALGIC 100 MG/ML SOLUTION BUVABLE	100 mg/ml	oral solution	TRAMADOL HYDROCHLORIDE
Napp Pharmaceuticals Ltd	IE	ZYDOL XL Tablets 150 mg	150 mg	q24h Tablets	Tramadol Hydrochloride