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

Rapifen
Alfentanil

BE/W/0003/pdWS/001

Rapporteur:	Belgium
Finalisation procedure (day 120):	28/02/2012
Date of finalisation of PAR	20/02/2013

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VIII
INN (or common name) of the active substance(s):	Alfentanil
MAH (s):	See section VIII
Pharmaco-therapeutic group (ATC Code):	Opioid anesthetics (N01AH02)
Pharmaceutical form(s) and strength(s):	Solution for injection, 0.5mg/ml

ABBREVIATIONS

ALF ALFENTANIL
TIVA TOTAL INTRAVENOUS ANESTHESIA
PONV POST OPERATIVE NAUSEA AND VOMITING

I. EXECUTIVE SUMMARY

This assessment report gives a summary of the clinical trials regarding the intravenous use of alfentanil (Rapifen®) in children. Alfentanil is an opioid analgesic with a rapid and short-lasting action. It is particularly suited as a narcotic analgesic for short procedures and outpatient surgery, but also as an analgesic supplement for longer procedures.

Summary of outcome

☐ No change

☒ Change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: sections 4.1 (slight change), 4.2, 4.6 and 5.2

☐ New indication: <section(s) xxxx, xxxx

II. RECOMMENDATION

SmPC and PL changes are proposed: See section VII p 29

III. INTRODUCTION

Janssen-Cilag submitted 33 articles related to paediatric studies for alfentanil, 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 articles do not influence the benefit risk for alfentanil and that there is no consequential regulatory action.

In addition, the following documentation has been included as an answer to the PdAR:

- An annex including SPC wording of sections 4.1, 4.2 and 4.4 related to the paediatric use of the medicinal product

IV. SCIENTIFIC DISCUSSION

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

Alfentanyl IV

IV.2 Non-clinical aspects

N/A

IV.3 Clinical aspects

1. Introduction

All clinical studies that were commented by the Applicant and additional ones that where found by the Rapporteur in the literature are summarised in three tables followed by important comments:

- pharmacokinetic studies with alfentanil in children
- pediatric studies with alfentanil IV (efficacy/safety – studies between 2000 and 2010)
- pediatric studies with alfentanil IV (efficacy/safety - studies before 2000).

The information given in these tables is focused on the dosing of alfentanil (loading and maintenance dose), and the age of the children.

2. Clinical studies

Pharmacokinetic studies

Pharmacokinetic studies with alfentanil in children			
Reference Year	**Number of patients Age**	**Dosing**	**Results**
FREID EB, 1994	34 3 to 131 months	ALF bolus 20microg/kg followed by 20microg/kg/h or Fentanyl	Fentanyl has a much larger half-life than alfentanil (15.9 versus 4.9 h), and also a much larger volume of distribution
den Hollander JM, 1992	6 : 4 – 11 months 6 : 1 – 9 years	Before surgery: 200microg/kg After surgery: 80microg/kg Infused in 10 minutes	Initial volume of distribution was smaller before than after surgery. Artenial blood pressure and heart rate decreased significantly after ALF was given
BROWNE BL, 1992	59 3 – 12 y	2 groups: - ALF loading dose 85 microg/kg and infusion 65 microg/kg/h - ALF loading dose 65 microg/kg and infusion 50 microg/kg/h	1st group: mean plasma ALF concentration of 279 (SD 78) nanog/ml 2nd group: mean plasma ALF concentration of 135 (SD 30) nanog/ml
WIEST DB, 1991	13 neonates (gestational age 37.6 ± 2.4 weeks)	ALF - loading dose: 8microg/kg - continous infusion: 2.5 – 10microg/kg/h	Mean elimination half-life was 4.14 ± 2.58h Both loading and maintenance dose were well tolerated
MARLOW, N, 1990	Part I: 22 preterm infants Study during the first 4 days of life Part II: 14 preterm infants	ALF 20microg/kg (part I) ALF 15-20microg/kg followed by 3-5 microg/kg/h (part II)	Part I: median half-life of ALF was 321 min (range: 64-1251min) Part II: steady state median ALF concentration of 54.5 nanog/ml (range: 7-73 nanog/nl)
KILLIAN A, 1990	5 preterm neonates at 26-35 weeks gestation 5 neonates at more than 35 weeks	ALF 25microg/kg	No difference between the two groups of children for volume of distribution, clearance and elimination half-life. Good hemodynamic tolerance
ORLIKOWSKI MB, 1990	7 neonates 5 infants (< 1 year)	ALF 50 microg/kg	Volume of distribution was increased in the neonates compared with the infants Blood pressure and pulse rose only in infants
DAVIS PS, 1989	15 3 months to 17y	ALF 50-100microg/kg	Cardiopulmonary bypass increase the volume of distribution and the elimination half-life of alfentanil
DAVIS PS, 1989	29 9 months to 15y	ALF 25-100microg/kg in children undergoing liver or kidney	No statistical difference among the 3 groups with respect to apparent volume of distribution , half-life of clearance

Pharmacokinetic studies with alfentanil in children			
Reference Year	**Number of patients Age**	**Dosing**	**Results**
		transplantation, compared to healthy children	
DAVIS PS, 1989	15 6 premature infants 9 older infants	Premature infants: 25microg/kg Older infants: 25-100microg/kg	Prolonged elimination half – life and larger volume of distribution in the premature infants
GORESKY GV, 1987	18 3 months – 14 y	50 or 120 microg/kg	Volume of distribution and elimination half-life were not different in infants less than 1 year of age when compared to older children. The increase of dose from 50 to 120 microg/kg resulted in a proportional increase in AUC (from 6784 nanog.min/ml to 15982 nanog.min/ml)
ROURE P, 1987	20 10 months – 6.5 y (compared with adult patients)	18 children: 20microg/kg 2 children : 50microg/kg	Elimination half – life was shorter in children than in adults

In the following table, the main pharmacokinetic data are summarised, for adults, infants and neonates (Dalens and Veyckemans, 2006).

	V_{dss} (L/kg)	**Clearance (mL/kg/min)**	**Half-life (h)**
Adult	0,45 ± 0,16	4,2 ± 1,7	1,3 ± 0,4
Child	0,16 ± 0,1	4,7 ± 0,6	0,6 ± 0,1
Infant	0,5 – 0,6	8,2 – 11,5	0,8 -1,3
Term neonate	0,8 ± 0,3	1,7 ± 0,5	5,5 ± 0,8
Premature	1 ± 0,39	2,2 ± 2,4	8,7 ± 5,1

V_{dss} : volume of distribution at steady-state

In total, **273** children were included in the pharmacokinetic studies with alfentanil.

The elimination half-life of alfentanil in adults is 1.5 h. The volume of distribution is comprised between 0.5 and 1.0l/kg. Following an IV injection of 50 microg/kg to 2 subjects, a mean plasma concentration of 540 nanog/ml was reported at 1 min, decreasing to 38 nanog/ml at one hour (Moffat, 2004). In adults concentrations of alfentanil between 35 and 50 nanog/ml are recommended for sedation during mechanical ventilation, although for analgesia during surgery concentrations of 200nanog/ml and higher are recommended. In the study of Goresky (1987), the increase of dose from 50 to 120microg/kg resulted in a proportional increase in AUC (from 6784nanog.min/ml to 15982nanog.min/ml). The volume of distribution and the elimination half-life were not different in infants less than 1 year of age when compared with older children but where higher in neonates and preterm neonates.

The concentrations of alfentanil that were measured in the study of Browne (1992), which involved children 3-12 years, suggest that alfentanil kinetics is not linear. In the study of Marlow (1990) using much lower doses of alfentanil (20 microg/kg followed by 5 microg/kg/h), the steady state median alfentanil concentrations were 54.5 nanog/ml, with no evidence of drug accumulation. However, there was great variability in peak serum concentration and clearance.

In three studies, it was concluded there was a difference in alfentanil pharmacokinetics between neonates and infants/older children (Orlikowski, 1990; Killian, 1990; Davis, 1989), notably a larger volume of distribution, a lower clearance and a prolonged half-life. However, Roure et al (1987) had demonstrated that elimination half-life of alfentanil was shorter in children than in adults. These differences are already emphasized in the SPC: plasma protein binding in newborns, in children and in adults are 75%, 85%, and 92%, respectively. The half-life is 146 ± 57 minutes in newborns and 40.2 ± 8.9 minutes in children. In adults, the half-life lies between 83 and 223 minutes (1.5 h in Moffat, 2004). Furthermore, in neonates the half-life is prolonged (see table here above from Dalens & Veyckemans).

Alfentanil is metabolized mainly via the cytochrome P450 CYP3A4. Potent CYP3A4 inhibitors such as azole derivatives, erythromycine, ritonavir may inhibit the metabolism of alfentanil. This could increase the risk of respiratory depression. If such inhibitors are administered together with alfentanil, it may be necessary to lower the dose of it. Fluconazole has reduced alfentanil clearance by 60%. With voriconazole the mean plasma clearance of alfentanil was decreased by 85% and its elimination half-life was prolonged from 1.5 h to 6.6 h. In vitro data indicate that ketoconazole and itraconazole may interact in a similar way (Stockley, 2010). Erythromycine increased the mean half-life of alfentanil in 6 subjects from 84 to 131 minutes and decreased its clearance by 26%. Ritonavir significantly reduced the clearance of both intravenous and oral alfentanil by about 3.7-fold and 10.5-fold, respectively. About the interaction between alfentanil and propofol, please refer to the comments about efficacy in the section 3 (Discussion on the clinical aspects).

In children one study was performed in 30 subjects to investigate the interaction between doxacurium and alfentanil compared to doxacurium and isoflurane (Kern, 1996). The children had received a loading dose of 20microg/kg alfentanil, followed (in one group) by a maintenance dose of 1 microg/kg/min. The total doxacurium dosage was statistically higher during alfentanil anesthesia than during isoflurane anesthesia (this is due to the synergistic muscle relaxant effect of isoflurane).

Efficacy/safety studies

In the first table, all recent paediatric studies are summarised (studies between 2000 and 2010).

Pediatric studies with alfentanil IV (efficacy/safety – studies between 2000 and 2010)				
Reference Year	**STUDY Type Comparator(s)**	**# of patients Age**	**Dosing**	**Results**
Kwak HJ, 2010.	2 groups: - O_2 group n = 25 - N_2O group n = 25	50 3-10 y	Starting dose ALF 14 microg./kg	ED50 ALF for successful intubation * O_2 group: 11.5 microg/kg (p53CI9.9-13.1) * N_2O group: 8.6 microg/kg (95% CI 7.4-9.8)
Goranović T, 2009.	2 groups: - ALF – propofol – rocuronium - ALF - propofol	208 2-12 y	ALF 20 microg./kg Propofol 2mg/kg Rocuronium 0.45mg/kg or ALF 20 microg/kg Propofol 3 mg/kg	No difference in: - intubation conditions - hemodynamic values between both groups Heart rate, systolic and diastolic pressure increased in both groups
Chiaretti A, 2009.	2 groups: - ALF/propofol - Ketamine/propofol Crossover study.	20 2-15 y	ALF 20 microg/kg Propofol 2 mg/kg Ketamine 1 mg/kg	- More respiratory depression in ALF group - No statistical difference of the pain Neuromediator levels (Nerve Growth Factor, Substitute P and enkephalins in CSF)
Kim JY, 2009	3 groups: - normal saline - ALF low dosage - ALF high dosage For annulling agitation	105 3-10 y	- ALF 10 microg/kg - ALF 20 microg/kg	Incidence of over agitation was lower in both ALF groups than in normal saline groups <u>No</u> difference between both ALF groups (PAED Pediatric Anesthesia Emergence Delirium)
Begec Z, 2009	2 groups: - ALF - Ketamine	18 3 months - 11 y	First: - ALF 20 microg/kg, or - Ketamine 0.5 microg/kg Than: Propofol 4 mg/kg	Time for return of spontaneous ventilation was prolonged with the ALF group (p=0.0004)

Pediatric studies with alfentanil IV (efficacy/safety – studies between 2000 and 2010)				
Reference Year	**STUDY Type Comparator(s)**	**# of patients Age**	**Dosing**	**Results**
Kwak HJ, 2009	3 groups: - ALF - Lidocaïne - ALF+lidocaïne	120 3-10 y	ALF 15 microg/kg	Incidence of painful propofol injections in the combination group (2-6%) significantly lower than in that of the ALF and lidocaïne groups (30% and 38.5%, respectively)
Rahman Al-Refai A., 2007	6 groups: - I and II remifentanil - III and IV ALF - V lidocaïne - VI normal saline	335 5-12 y	ALF Group III: 15 microg/kg Group IV: 20 microg/kg	Pretreatment with IV remifentanil 0.5 microg/kg or ALF 15 microg/kg and 20 microgr/kg were equally effective in reducing painful propofol injection
Oh AY, 2007	4 groups: - Saline - Remifentanil - ALF - Fentanyl	164 1-14 y	ALF 10 microg/kg	Efficacy in reducing withdraw movement associated with the injection of rocuromium Remifentanil was the most effective, followed by ALF
Bartolek D, 2007	3 groups: Propofol 2, 2.5 or 3 mg/kg (+ rocuronium)	111 6-9 y	ALF 20 microg/kg	Induction dose of 2.5 mg/kg propofol preceded by 20 microg/kg ALF in addition to reduced-dose rocuronium (0.45mg/kg) is the optimal pediatric induction dose
Bülent Antmen, 2005	4 groups: - Remifentanil - ALF - Remifentanil-midazolam -ALF-midazolam	80 5-16 y	ALF 20 microg/kg	No statistical difference between sedation and the CHEOPS scores of the 4 groups. No safety issue
Babre F, 2005	ALF + propofol For pediactric bronchoscopy	30 3.2 ± 3.8 y	Induction dose: ALF 10 microg/kg	Satisfactory anesthesia with few side effects
von Heijne M, 2004	ALF as additional analgesic when EMLA® and lidocaïne were not coefficient for bone marrow aspiration	28 2-16 y	Intermittent doses of 2 – 3 microg/kg ALF	Propofol + ALF was preferred by patients' parents

Pediatric studies with alfentanil IV (efficacy/safety – studies between 2000 and 2010)				
Reference Year	**STUDY Type Comparator(s)**	**# of patients Age**	**Dosing**	**Results**
Ganidagli S, 2003	2 groups: Remifentanil or ALF combined with propofol and mivacurium	60 2-14 y	ALF: Loading dose: 50 microg/kg Maintenance infusion: 1 microg/kg/min	Remifentanil provides a more rapid recovery and adequate postoperative analgesic for pediatric abdominal surgery, compared with ALF. No difference between the groups with regard to intraoperative dysrhythmias, PONV or hypoxia

In the second table, all clinical studies published before 2000 are briefly summarised.

Pediatric studies with alfentanil IV (efficacy/safety - studies before 2000)				
Reference Year	**STUDY Type Comparator(s)**	**# of patients Age**	**Dosing**	**Results**
Da Conceiçao MS, 1999	Open study Bolus and maintenance of ALF +propofol	500 2-7 y	Bolus dose ALF: 14microg/kg New dose of 20 microg/kg if needed	TIVA satisfactory in children, with good hemodynamic stability
NG KP, 1999	Alfentanil compared with suxamethonium in children under halothane anaesthesia	40 Mean: 4.6 y	ALF dosage: 20 microg/kg	Alfentanil blunted the increase in mean arterial pressure and heart rate after intubation.
Erlacher W, 1998	3 groups: - ALF+propofol low dose - ALF+propofol high dose - Thiopentone+succinylcholine	60 children < 25kg	ALF 20 microg/kg	Intubation conditions excellent in all groups
Küçükyavuz Z, 1998	2 groups: - ALF+propofol - fentanyl+propofol	30 3.5-9 y	ALF 20 microg/kg	No difference on intubation scores between both groups – good hemodynamic stability
Robinson DN, 1998	2 groups: -ALF+propofol -remifentanil+propofol	40 2-12 y	ALF 15 microg/kg	No difference on intubation conditions between both groups
Belzarena SD, 1996	2 groups - ALF + lidocaïne - succinylcholine	60 5-11 y	ALF 20 microg/kg	No difference in the laryngoscopy conditions No case of bradycardia in the ALF group, 30% bradycardia in the succinycholine group
Senel AC, 1996	3 groups - ALF low dose - ALF high dose - atracurium	45 4-14 y	ALF Low dose 10microg/kg High dose 20microg/kg	No difference in intubation conditions between groups

Pediatric studies with alfentanil IV (efficacy/safety - studies before 2000)				
Reference Year	**STUDY Type Comparator(s)**	**# of patients Age**	**Dosing**	**Results**
McConaghy P, 1994	3 groups: - ALF low dose - ALF medium dose - ALF high dose + propofol	60 3-12 y	ALF 5 microg/kg, 10 microg/kg, or 15 microg/kg	Intubation was successful in 5% of patients with ALF medium or high dose and in 70% of patients with ALF low dose
Spear RM, 1994	4 groups: With ALF + propofol	35 11 y (mean age)	ALF: - 30 - 40 microg/kg - 50 - 60	Excellent intubation conditions in all groups. No case of bradycardia or hypotension
Ayala-Sandoval S, 1993	3 groups: - ALF - fentanyl - lidocaïne	180 1-15 y	ALF 50microg/kg	Alfentanil has faster onset of action than Fentanyl Good cardiovascular stability in both ALF and Fentanyl
Hiller A, 1993	3 groups: - ALF low dose - ALF high dose - ALF + lidocaïne (low dose) + propofol	45 1-3 y 45 4 y and older	ALF Low dose: 20 microg/kg High dose: 40microg/kg	Intubating conditions significantly better in the ALF high dose group compared to the low dose group, in children aged 1-3. In the older age the differences between groups were not significant. BRADYCARDIA was observed with the ALF group
Veyckemans F, 1992	Dose of ALF Propofol needed to ensure prevention of painful procedures in children with cancer or hematologic disease	111 6-240 months	ALF 2-5microg/kg as first dose	Mean dose of ALF needed: 4.46 microg/kg (SD 1.48)
Rautiainen P, 1992	ALF continuous infusion after Fontan operation	14 5-20 y		ALF mean induction dose: 4.4 ± 2.7microg/kg ALF mean dose maintenance dose: 10.3 ± 8.6microg/kg

Pediatric studies with alfentanil IV (efficacy/safety - studies before 2000)				
Reference Year	**STUDY Type Comparator(s)**	**# of patients Age**	**Dosing**	**Results**
Rosen DA, 1992	Open study ALF+propofol	57 mean age: 1.3 y ± 6.2	ALF 20 microg/kg	ED50 to achieve eye closure was 13microg/kg for ALF No nausea or vomiting was noted
Davis PJ, 1991	- Bolus + continuous infusion of ALF + N_2O - Halothane+nitrous oxide	40 2-12 y	ALF bolus: 100 microg/kg Maintenance: 2 microg/kg/min	Hemodynamic stability was maintained in both groups. Higher occurrence of PONV in children treated with ALF
Burtles R, 1991	Different doses of ALF were compared together with methohexitone for dental anaesthesia	57 4-16 y	Alf 2.5, 5.0, 7.5 and 10 microg/kg	Incidence of crying was significantly lower in the group receiving the highest alfentanil dose, i.e. 10 microg/kg.
Rymer DB, 1990	Children under halothane 2 groups: - Stop halothane + ALF - Halothane maintained	30 Exact age not specified	ALF 50 microg/kg With supplemental boluses of 10 microg/kg	Adequate analgesia in both groups Range of ALF boluses 1.5-2.5microg/kg/min with hemodynamic stability
Skubella U, 1989	2 groups - Ethrane inhalation - ALF combination (succinylcholine)	25 3-10 y	ALF 16.6 microg/kg followed by 33.4 microg/kg	Good hemodynamic stability and analgesic efficacy of ALF
Piette Ch, 1982	Open study ALF + succinylcholine + droperidol	78 1-11 y	ALF Induction dose: 10-50 microg/kg Maintenance dose: 1-2microg/kg/min	Good analgesic in 92% of the cases. Secondary vagal effects necessitate primary administration of a vagolytic agent

In total, these studies involved **1329** (studies between 2000 and 2010) and **1455** (studies before 2000) thus in total **2784** children aged 1 -14 years. In only two studies (Begec, 2009; Veyckemans, 1992), children younger than 1 year were present. Generally, alfentanil was used in combination with propofol in children undergoing adenotonsillectomy or other elective surgery. Other drugs were also used, as rocuronium, lidocaine…The combination of alfentanil with propofol is particularly appropriate. Indeed, low concentrations of alfentanil dramatically reduce the need for propofol. However, even very high concentrations of alfentanil cannot completely eliminate the need for propofol to maintain adequate anesthesia (Evers & Maze, 2004). Experiments suggest that at high propofol concentrations, low-dose alfentanil is contributing primarily an analgesic effect to the overall anesthetized state, whereas at lower propofol concentrations, the higher alfentanil concentration required is also making important contributions to the hypnotic effect. Furthermore, alfentanil (and lidocaine) has been demonstrate to prevent pain on propofol injection (Kwak, 2009), at the dose of 15 microg/kg. The combination of alfentanil and lidocaine was significantly better for this purpose than each drug alone.

The **range of alfentanil dose** was comprised between 10 microg/kg and 100 microg/kg (loading dose), and between 1 microg/kg/min and 2 microg/kg/min for the maintenance dose. In the most recent study (Kwak, 2010), the bolus dose of alfentanil for each subject was determined by the response of the previously tested subject by using the up-and-down sequential allocation method of Dixon and Massey (2 microg/kg as a step size). The first dose of alfentanil was 14 microg/kg. If intubation failed, the alfentanil dose was increased by 2 microg/kg. If it was successful, it was then decreased by 2 microg/kg. The objective of the study was to determine the optimal bolus dose of alfentanil for successful tracheal intubation during sevoflurane induction with and without nitrous oxide. As it was found in the results (see in the table here above), addition of nitrous oxide 60% in oxygen reduced the effective alfentanil dose by 25%.

Important remark: in the study of Piette (1982), the English translation from the French text showed major mistakes, especially for the units used to express all alfentanil dosages: micrograms were changed in milligrams!

3. Discussion on clinical aspects and conclusion

About the optimal intravenous dosing of alfentanil

For efficacy

The minimal effective dose of alfentanil in children is 10 microg/kg as bolus dose, as it can be concluded from the following studies: Senel, 1996; McConaghy, 1994; Oh, 2007; Babre, 2005; Kim, 2009. This 10 microg/kg dose appears suitable for surgery or procedures (bone marrow aspiration, biopsy) of short duration. A lower dose, 5 microg/kg (McConaghy, 1994) was used with propofol before intubation, but was less effective than the 10 microg/kg dose. Lower intermittent doses of 2-3 microg/kg were also used as an additional analgesic when Emla® and lidocaine were not sufficient for bone marrow aspiration (von Heijne, 2004). Finally, Veyckemans et al (1992) showed that the mean alfentanil dose to ensure prevention of painful procedures in children with cancer or haematological disease was 4.46 microg/kg (SD 1.48). At the present time this author uses between 5 and 10 microg/kg associated with propofol for painful procedures.

The ratio alfentanil/propofol is frequently used before intubation. The ratio 20 microg/kg alfentanil/ 2 mg/kg propofol is effective and ensures good intubation conditions (Goranovic,

2009; Chiaretti, 2009). However, the dose of 15 microg/kg alfentanil was even effective than that of 20 microg/kg (Rahman Al-Refai, 2007) in reducing pain on propofol injection.

The maximal doses used in the studies are comprised between 40 and 100 microg/kg.

Regarding elective surgical procedures, tracheal intubation could be achieved with propofol preceded by alfentanil (or another opioid) without the use of muscle relaxant (Bartolek, 2007), or with a reduced dose of rocuronium. This latter author showed that an induction dose of 2.5mg/kg propofol preceded by 20 microg/kg of alfentanil in addition to reduced-dose rocuronium (0.45 mg/kg) is the optimal pediatric induction dose of propofol for obtaining the best intubating conditions.

The infusion dose of alfentanil was comprised between 1 and 2 microg/kg/min in the clinical studies. The recommended infusion rate in the Belgian SPC is 1 microg/kg/min in order to maintain analgesia when surgery is more prolonged.

For safety

In the clinical studies using doses of alfentanil between 10 and 60 microg/kg, no serious adverse effects were noted. All children showed stable haemodynamic values. No case of bradycardia or hypotension was reported, but in the study of Hiller (2003), especially in children aged > 4 years. In the only study where a high dose of 100 microg/kg alfentanil was used (Davis, 1991), a higher incidence of PONV occurred. In all the studies presented here above, the children treated with alfentanil showed a good haemodynamic stability. However, when higher doses of alfentanil were administered (200 microg/kg in the study of den Hollander, 1992), arterial blood pressure and heart rate decreased significantly after alfentanil was given.

Pokela et al (1992) evaluated the toxicity of alfentanil in neonates. Alfentanil (mean dose 11.7 microg/kg – range 9-15) was given intravenously to 20 mechanically ventilated critically ill newborn infants during the first three days of life before treatment procedures. Nine neonates had mild or moderate muscle rigidity, which had little or no effect on ventilation. Four neonates had severe rigidity and jerking comparable to convulsive activity, transient impairing ventilation and oxygenation for 5-10 minutes.

References

Books

Dalens B, Veyckemans F. Anesthésie pédiatrique. Sauramps Médical 2006, 1ère Edition.

Evers AS, Maze M. Anesthetic pharmacology. Churchill Livingstone 2004.

Martindale. The complete drug reference 36th Edition 2009.

Miller's anesthesia. Churchill Livingstone 5th Edition 2006.

Moffat AC, Osselton MD et al. Clarke's analysis of drugs and poisons. The Pharmaceutical Press 3rd Edition 2004.

Articles

1. Antmen B, Sasmaz I et al. Safe and effective sedation and analgesia for bone marrow aspiration procedures in children with alfentanil, remifentanil and combinations with midazolam. Pediatr Anesth 2005; 15: 514-519.
2. Ayala-Sandoval S, Gonzalez-Guzman MdP et al. Alfentanyl versus fentanyl in total intravenous anaesthesia for ambulatory paediatric patients. Rev Mex Anest 1993; 16: 214-220.
3. Belzarena SD. Nasal intubation in paediatric patients. Comparison between a combination of alfentanil and lidocaine versus succinylcholine. Rev Bras Anestesiol 1996; 46(5): 323-328.
4. Babre F, Bordes M et al. Evaluation of an anaesthetic protocol associating propofol and alfentanil for paediatric fiberoptic bronchoscopy. Eur J Anaesthesiol 2005; 22 (Suppl 34): 145.
5. Bartolek D, Lajtman Z et al. The optimal pediatric induction dose of propofol in combination with reduced-dose rocuronium and alfentanil for day-case tonsillectomy in children. Int J Ped Otorhinol 2007; 71: 1873-1881.
6. Begec Z, Demirbilek S et al. Ketamine or alfentanil administration prior to propofol anaesthesia: the effects on ProSeal laryngeal mask airway insertion conditions and haemodynamic changes in children. Anaesthesia 2009; 64: 282-286.
7. Björkman S. Prediction of cytochrome P450-mediated hepatic drug clearance in neonates, infants and children. Clin Pharmacokinet 2006; 45(1): 1-11.
8. Browne BL, Prys-Roberts C et al. Propofol and alfentanil in children : infusion technique and dose requirement for total IV anaesthesia. Br J Anaesth 1992; 69(6): 570-576.
9. Burtles R. Alfentanil with methohexitone in paediatric dental anaesthesia. J Dent 1991; 19(3): 192-194.
10. Chiaretti A, Ruggiero A et al. Propofol/alfentanil and propofol/ketamine procedural sedation in children with acute lymphoblastic leukaemia: safety, efficacy and their correlation with pain neuromediator expression. Eur J Cancer Care(Engl) 2010; 19(2): 212-220.
11. da Conceiçao MJ, Cidral E et al. Total intravenous anaesthesia in paediatric patients: clinical study. Rev Bras Anestesiol 1999; 49: 304-308.
12. Davis PJ, Chopyk JB et al. Continuous alfentanil infusion in pediatric patients undergoing general anesthesia for complete oral restoration. J Clin Anesth 1991; 3: 125-130.
13. Davis PJ, Stiller RL et al. Effects of cardiopulmonary bypass and hypothermia on alfentanil pharmacokinetics in infants and children during cardiac surgery. Unpublished confidential report, 1989.
14. Davis PJ, Stiller RL et al. Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. Anesth Analg 1989; 68: 579-583.
15. Davis PJ, Killian A et al. Pharmacokinetics of alfentanil in newborn premature infants and older children. Dev Pharm Ther 1989; 13: 21-27.
16. den Hollander JM, Hennis PJ et al. Pharmacokinetics of alfentanil before and after cardiopulmonary bypass in pediatric patients undergoing cardiac surgery: part I. J Cardiothor Vasc Anesth 1992; 6(3): 308-312.
17. Dixon WJ, Massey FJ. Introduction to statistical analysis. McGraw-Hill 1983 4th Ed; 426-441 (cited in Kwak, 2010).
18. Erlacher W, Kontaratos M et al. Intubation without muscle relaxation. Alfentanil/propofol as an alternative induction regime for children. Anesthesiology 1998; 89(3A): abstract A1316.
19. Fiset P, Mathers L et al. Pharmacokinetics of computer-controlled alfentanil administration in children undergoing cardiac surgery. Anesthesiology 1995; 83(5): 944-955.

20. Freid EB, Miles MV et al. Prolonged continuous infusions of fentanyl or alfentanil in critically ill children. Anesthesiology 1994; 81(3A): Abstract A257.
21. Ganidagli S, Cengiz M et al. Remifentanil vs alfentanil in the total intravenous anaesthesia for paediatric abdominal surgery. Paediatr Anaesth 2003; 13: 695-700.
22. Goranovic T, Milic M et al. Haemodynamic changes and intubating conditions during tracheal intubation in children under anaesthesia : a comparative study of two induction regiments. Med Glas 2009; 6(1): 104-111.
23. Goresky GV, Koren G et al. The pharmacokinetics of alfentanil in children. Anesthesiology 1987; 67: 654-659.
24. Hiller A, Klemola M et al. Tracheal intubation after induction of anaesthesia with propofol, alfentanil and lidocaine without neuromuscular blocking drugs in children. Acta Anaesthesiol Scand 1993; 37: 725-729.
25. Hynynen M. Binding of fentanyl and alfentanil to the extracorporeal circuit. Acta Anaesthesiol Scand 1987; 31: 706-710.
26. Kern C, Tassonyi E et al. Doxacurium pharmacodynamics in children during volatile and opioid-based anaesthesia. Anaesthesia 1996; 51: 361-364.
27. Killian A, Davis PJ et al. Influence of gestational age on pharmacokinetics of alfentanil in neonates. Dev Pharmacol Ther 1990; 15: 82-85.
28. Kim JY, Chang J et al. Post-induction alfentanil reduces sevoflurane-associated emergence agitation in children undergoing an adenotonsillectomy. Acta Anaesthesiol Scand 2009; 53: 678-681.
29. Kliegman, Behrman et al. Nelson textbook of pediatrics. Saunders Elsevier 18th Edition 2007.
30. Küçükyavuz Z, Karsli B et al. Comparison of alfentanil/propofol and fentanyl/propofol in induction during intubation without muscle releaxants in children. Türk Anest Rean Cem Mecmuzasi 1998; 26: 34-38.
31. Kwak HJ, Kim JY et al. Optimal bolus dose of alfentanil for successful tracheal intubation during sevoflurane induction with and without nitrous oxide in children. Br J Anaesth 2010; 104(5): 628-632.
32. Kwak HJ, Min SK et al. Prevention of propofol-induced pain in children: combination of alfentanil and lidocaine vs alfentanil or lidocaine alone. Br J Anaesth 2009; 103(3): 410-412.
33. Marlow N, Weindling AM et al. Alfentanil pharmacokinetics in preterm infants. Arch Dis Child 1990; 65: 349-351.
34. McConaghy P, Bunting HE. Assessment of intubating conditions in children after induction with propofol and varying doses of alfentanil. Bf J Anaesth 1994; 73: 596-599.
35. NG KP, Wang CY. Alfentanil for intubation under halothane anaesthesia in children. Paediatr Anaesth 1999; 9(6): 491-494.
36. Oh AY, Seo KS et al. Prevention of withdrawal movement associated with injection of rocuronium in children: comparison of remifentanil, alfentanil and fentanyl. Acta Anaesthesiol Scand 2007; 51: 1190-1193.
37. Orlikowski MB, Heykants J et al. Pharmacokinetics of alfentanil in neonates and infants. Unpublished confidential report, 1990.
38. Piette Ch. Alfentanil administered via perfusion to children weighing 10 to 30 kg. Unpublished report, Belgium, 1982 (translation).
39. Pokela ML, Ryhanen PT et al. Alfentanil-induced rigidity in newborn infants. Anesth Analg 1992; 75(2): 252-257 (abstract).
40. Rahman Al-Refai A, Al-Mujadi H et al. Prevention of pain on injection of propofol: a comparison of remifentanil with alfentanil in children. Minerva Anestesiol 2007; 73(4): 219-223.
41. Rautiainen P. Alfentanil sedation for cardiac catheterization of children with Fontan shunts. Can J Anaesth 1992; 39(9): 944-948.

42. Robinson DN, O'Brien K et al. Tracheal intubation without neuromuscular blockade in children : a comparison of propofol combined either with alfentanil or remifentanil. Paediatr Anaesth 1998; 8: 467-471.
43. Rosen DA, Rosen KR et al. Alfentanil and propofol for bone marrow procedures: a dose-response study. Anesthesiology 1992; 77(3A): Abstract A1186.
44. Roure P, Jean N et al. Pharmacokinetics of alfentanil in children undergoing surgery. Br J Anesth 1987; 59: 1437-1440.
45. Rymer DB, Davis PJ et al. Safety and efficacy of alfentanil in children less than one year of age. Anesth Analg 1990; 70: S1-S450.
46. Senel AC, Aktürk G et al. Comparison of intubation conditions under propofol in children. Middle East J Anesth 1996; 13(6): 605-611.
47. Spear RM, Rodarte A et al. Propofol/alfentanil for rapid intravenous induction and tracheal intubation without muscle relaxant in children. Anesthesiology 1994; 81(3A): abstract 1327.
48. Skubella U, Hucke H. Alfentanil combination anaesthesia in adenotonsillectomy in childhood-a comparison with ethrane inhalation anaesthesia. Anästhesie, Intensivtherapie, Notfallmedizin 1989; 24(6): 362-367.
49. Stockley's drug interactions. The pharmaceutical Press 9th Edition 2010.
50. Veyckemans F, Versailles H et al. Evaluation of alfentanil/propofol for pediatric painful procedures. Anesthesiology 1992; 77(3A): abstract 1185.
51. von Heijne M, Bredlöv B et al. Propofol or propofol-alfentanil anesthesia for painful procedures in the pediatric oncology ward. Pediatr Anesth 2004; 14: 670-675.
52. Wiest DB, Ohning BL et al. The disposition of alfentanil in neonates with respiratory distress. Pharmacotherapy 1991; 11(4): 308-311.
53. Wilson AS, Stiller RL et al. Fentanyl and alfentanil plasma protein binding in preterm and term neonates. Anesth Analg 1997; 84(2): 315-318 (abstract).

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The indication of alfentanil as" a opiate analgesic in general as well as intravenous adjuvant to regional anaesthesia and for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures" can be accepted for children aged more than 3 months.

The recommended dosages for alfentanil as an analgesic (i.e. to supplement propofol or inhalation anaesthesia) in infants and children should be modified as follows:

- as single bolus IV injection: 10 to 20 microg/kg alfentanil. Supplemental boluses of 5 to 10 microg/kg/15 min can be administered.

- or an infusion dose of 1 to 2 microg/kg/min starting after the bolus injection can be used.

These dose ranges are considered to have a positive benefit/risk balance for the administration of alfentanil in infants and children.

For the indication as an "anaesthetic induction agent" the maximum dose should not exceed 25 to 75 microg/kg as an intravenous bolus dose for adults (Miller, 2006). However, this high

dose of alfentanil used for general anaesthesia should be justified as it is no longer used in the daily practice.

For all dosages, assisted ventilation is required.

- **Recommendation**

The following SPC sections should be adequately modified:

- Indications: to delete or to justify the induction dose for general anaesthesia.

- Posology: to revise the bolus and infusion dose for infants and children (see the details here above in the overall conclusion).

- Pharmacokinetic properties: to amend the half-life in neonates, which maybe longer than 146 minutes: following Dalens a Veyckemans (2006), this half-life is 5.5 ± 0.8 hours.

Comment DE

The Federal Institute for Drugs and Medical Devices does not agree with the overall conclusions of the Rapporteur for the following reasons:

Specific comments:

1. In DE alfentanil is approved for the use as "analgesic agent in induction and maintenance of general anesthesia" (wording in section 4.1). It is not approved as an intravenous adjuvant to regional anesthesia. An overview of the use of alfentanil as an intravenous adjuvant to regional anesthesia is missing and should be presented with a proposal of SPC wording if appropriate.
2. In DE the use of alfentanil in children below the age of 1 year is contraindicated. Only 2 studies were presented including children < 1y. A more detailed data based discussion about the extent of use, dosing and safety in this population should be presented.
3. A statement about the use of alfentanil for analgesia in painful procedures in children should be submitted.
4. In the UK SPC in section 4.2 a recommendation for the use in intensive care is given (little experience in children). A statement regarding the knowledge of the use in pediatric intensive care should be made as well.

General comments:
As SmPC wording varies between Member States, concrete proposals for the wording regarding sections 4.1, 4.2, 4.3, 4.4 and 5.2 according to the current SmPC Guideline (2009) and a proposal for a PL wording should be submitted.

Comment SE

The Medical Products agrees partly with the overall conclusion of the Rapporteur. However, the Medical Products Agency do not agree with the proposed dosing recommendation and has the following point for consideration by the Rapporteur before adopting final recommendations for

the SmPC:

The data do not strongly indicate that the maintenance infusion dose of alfentanil in children should be increased from the present day recommendation in SE (as well as in BE) 1 microg/kg/min to 1-2 microg/kg/min. This conservative view is in line with the general paediatric posology, where the doses are lower than for the adult population.

Furthermore, the following points should be addressed concerning section 5.2 in the SmPC: Pharmacokinetic information should be included for infants and children as far as the data is available, *i.e.* for all age groups. The data should be presented with the actual studied age range and the number of individuals studied. Clearance and volumes should be given per kg body weight.

Comments NL:

The general view of The Medicines Evaluation Board of The Netherlands on the benefit/risk is positive and we agree on the recommendations of the Rapporteur. With regard to the use in newborn and premature infants, it is recommended to request the company to provide dose recommendations for the infants < 3 months (based on PK modelling). We recommend to await the company's response and proposal for the dose advice in the SPC for the youngest age group.

Furthermore, we recommend some additional changes in section 4.2 and 4.6 of the SPC. Specific comments address the following issues:
1) Dose recommendations for the newborn and premature.
2) Warning that assisted ventilation should be used.
3) The need for myorelaxants in the youngest age group.
4) Warning about the use of alfentanil during pregnancy and delivery.

The following text is proposed:

4.2 Posology and method of administration
The dosage of Rapifen should be individualised. Factors that play a role here are age, bodyweight, physical status, underlying pathological condition, use of other drugs, type of anaesthesia, and type and duration of surgery. RAPIFEN can be administered to patients of any age.
The initial dose should be reduced in the elderly and in debilitated patients. In children between 3 and 17 years the dose might need to be higher due to shorter half life. In infants, neonates and premature babies, the dose should be reduced taking into account the prolonged half life in these age categories.

Short term procedures or induction in anaesthesia
For procedures of less than 10 minutes an intravenous bolus injection of 10 to 20 µg/kg bodyweight is sufficient.
If the procedure is of longer duration, supplemental doses of 5 to 10 µg/kg bodyweight can be administered every 10 to 15 minutes, where necessary.

In newborn and preterm infants the dose has to be adjusted due to the longer half life, reduced clearance and prolonged exposure. The recommended doses are presented in the table below.

	Clearance (mL/kg/min)	Half-life (h)	Bolus dose (µg/kg)
Adult	4,2 ± 1,7	1,3 ± 0,4	To be filled in with appropriate dose recommendations
Child	4,7 ± 0,6	0,6 ± 0,1	To be filled in with appropriate dose recommendations
Infant	8,2 – 11,5	0,8 -1,3	To be filled in with appropriate dose recommendations
Term neonate	1,7 ± 0,5	5,5 ± 0,8	To be filled in with appropriate dose recommendations
Premature	2,2 ± 2,4	8,7 ± 5,1	To be filled in with appropriate dose recommendations

Maintenance of analgesia in general anaesthesia
To maintain analgesia RAPIFEN can also be administered in an infusion. The recommended infusion rate is 1.0 to 2.0 µg alfentanil/kg body weight/min. The application via a perfusor is considered to be the best way of application (for maintenance).

For all dosages assisted ventilation is required.

4.6 Pregnancy and lactation
IV administration during childbirth (including Caesarean section) is not recommended, because Rapifen crosses the placenta and because the foetal respiratory centre is particularly sensitive to opioids. If Rapifen is administered nevertheless, this should be done only in conditions were artificial ventilations can be applied instantly. The use of antidotes is recommended; in case the half-life of antidote is shorter than the half-life of alfentanil repeated administration of the antidote has to be considered.

Answers to the specific comments from Germany, Sweden and the Netherlands

Preliminary note

For all references (books and articles), please go back to Rapporteur's preliminary assessment report or to the list in annex 1 of this report. Only the new references are mentioned in this report.

- **About the indications**

In the SPC of the reference product Rapifen®, the second indication states that alfentanil can be used as adjuvant to regional anaesthesia for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures.

The indication "adjuvant to regional anaesthesia" is accepted by the major authors in the field of pediatric anesthesia (Dalens & Veyckemans, 2006; Evers & Maze, 2004; Miller, 2006). However, the word "adjuvant" should be replaced, as it doesn't reflect the reality. Alfentanil is actually used as an analgesic drug in association with regional anesthesia (comment from the Belgian peer-reviewer, professor in pediatric anesthesiology).

In the pediatric studies, alfentanil was used together with propofol as anesthesia for the following surgical interventions:

- tonsillectomy or other ear, nose and throat surgery (most studies)
-bronchoscopy (Babre, 2005)
-abdominal surgery (Rymer, 1990, Ganidagli, 2003)
-bone marrow biopsies and lumbar puncture (se below)
-cardiopulmonary bypass and congenital heart disease
-respiratory disorders
-intensive care procedures (Davis, 1989)
-orthopedic surgery (Roure, 1987).

The use of alfentanil in regional anesthesia has been reported in the following studies in adult patients:

-Fang, 2006: the combination propofol-alfentanil-lidocaine 2% (6-2-2 mixture) was used in 89 adult patients undergoing ophthalmic surgery with regional block and monitored anesthesia. This novel mixture provided adequate analgesia and sedation as well as hemodynamic stability.

-Kurt, 2002: addition of alfentanil to lidocaine solution in 33 adult patients for intravenous regional anesthesia gave no clinical benefit for regional anesthesia of the arm.

-Arroyo, 1995: 90 patients were treated with continuous alfentanil infusion, which was considered to provide adequate analgesia for lithotripsy.

In children, alfentanil was mostly used with propofol. Discussion on the ratio of alfentanil/propofol can be found in chapter 3. Discussion on clinical aspects of the Rapporteur's Assessment Report. Low concentrations of alfentanil dramatically reduce the need for propofol, but even very high concentrations of alfentanil cannot completely eliminate the need for propofol to maintain adequate anesthesia. The pharmacodynamic synergy of both drugs suggests that at high propofol concentrations, low-dose alfentanil is contributing primarily as an analgesic effect to the overall anesthetized state, whereas at lower propofol concentrations, the higher alfentanil concentration required is also making important contributions to the hypnotic effect (in women patient)(Vuyk, 1995). In the great majority of the studies presented in the tables (see Assessment Report), alfentanil was used successfully with propofol for anesthesia in children. The hemodynamic stability was maintained with this combination while adequate analgesia was obtained. Excellent intubation conditions were also obtained when alfentanil was combined with propofol. Low dose alfentanil regimens (10 – 20 microg/kg alfentanil) yielded intubation conditions even favorable than high dose alfentanil treatments.

Alfentanil is used with propofol for analgesia in painful procedures in children. Kwak et al (2009; 2010) proposed optimal doses of alfentanil for successful tracheal intubation in children. Alfentanil was also used for other painful procedures: bone marrow aspiration, lumbar puncture

(Rosen, 1992; Veyckemans, 1991; Antmen, 2005; von Heijne, 2004, Chiaretti, 2009). Alfentanil (dose: 20 microg/kg) was also considered as an effective treatment (with ketamine) for the treatment of pain after hypospadias repair surgery in children (Ozbek, 2002).

Alfentanil has been used in children in intensive care settings (Davis, 1989; Bartolek, 2007; Rahman Al-Refai A, 2007). In the RCPCH (2003), it is stated that alfentanil is an analgesic for patients in intensive care on assisted ventilation.

For the treatment of painful procedures in children and in intensive care settings, the dosage recommendations for alfentanil are the same as for "adjuvant to regional anesthesia" (see "overall conclusion" of chapter V of the Rapporteur's Assessment Report).

To conclude, the Rapporteur proposes the following rewording of the indications: alfentanil is indicated for use as:

- An anesthetic induction agent
- A narcotic analgesic in association with general or regional anesthesia or for painful procedures.
- An analgesic for patients in intensive care on assisted ventilation.

- **About dosage in function of age**

In the RCPCH (Medicines for Children- Royal College of Paediatrics and Child Health – UK 2003) and in the Nelson Textbook of Pediatrics (2007), alfentanil is proposed without age limits, thus also for neonates.

In the clinical studies, most children were aged 1 to 12 years. In the following studies, younger children were involved:
-from 3 months of age: Begec (2009), Freid (1994), Davis (1989), Goresky (1987)
-from 4 months of age: den Hollander (1992)
-from 6 months of age: Veyckemans (1992)
-neonates: Wiest (1991), Marlow (1990), Killian (1990), Orlikowski (1990), Davis (1989).

The following proposals are made by the Rapporteur:

- Dose recommendations should be proposed by the Applicant for the infants younger than 3 months (based on the studies and on the pharmacokinetic data).

- The maintenance infusion dose of alfentanil in children should remain 1microg/kg/min and not increased to 1-2 microg/kg/min, as there are not enough data to support this dose increase. The dose of 1 microg/kg/min of alfentanil was demonstrated by Ganidagli et al (2003) to be an effective and safe analgesic in anesthesia for children undergoing abdominal surgery.

- Pharmacokinetic information should be added for infants and children for all age groups (in section 5.2 of the SPC).

- The Applicant should address the need of myorelaxants in the youngest aged group as well as the need for assisted ventilation for all indications.

Additional information should come in section 4.2: “In children between 3 and 17 years the dose might need to be higher due to shorter half-life. In infants, neonates and premature babies, the dose should be reduced taking into account the prolonged half-life in these age categories” (see table from Dalens and Veyckemans, 2006).

- **About pregnancy and lactation**

The Rapporteur agrees on the following text: “IV administration during childbirth (including Caesarean section) is not recommended, because Rapifen® crosses the placenta and because the fetal respiratory rate is particularly sensitive to opioids. If Rapifen® is administered nevertheless, there should be done only if artificial ventilation can be applied immediately. The use of antidotes is recommended; if the half-life of antidote is shorter than the half-life of alfentanil, repeated administration of the antidote has to be considered”.

Additional remark from the Rapporteur on breastfeeding: it is not needed to wait 24 hours for resuming breastfeeding, because alfentanil has a half-life of 1.3 hours in adults. To wait 10 hours (i.e. about 7 half-lives) is definitively sufficient.

Final remark

Concrete proposals for the PIL will follow adoption of the definitive text for the SPC. The Applicant should propose a new version of the PIL which takes all SPC remarks into account.
Final remark

Concrete proposals for the PIL will follow adoption of the definitive text for the SPC. The Applicant should propose a new version of the PIL which takes all SPC remarks into account.

References

1. Arroyo CS, Michaels EK et al. Use of continuous-infusion alfentanil for analgesia during spark-gap lithotripsy. J Endourol 1995; 9(1): 41-43.
2. Fang ZT, Keyes MA. A novel mixture of propofol, alfentanil, and lidocaine for regional block with monitored anesthesia care in ophthalmic sugery. J Clin Anesth 2006; 18(2): 114-117.
3. Kurt N, Kurt I et al. Effects of adding alfentanil of atracurium to lidocaine solution for intravenous regional anaesthesia. Eur J Anaesthesiol 2002; 19(7): 522-555.
4. Ozbek H, Bilen A et al. The comparison of caudal ketamine, alfentanil and ketamine plus alfentanil administration for postoperative analgesia in children. Paediatr Anaesth 2002; 12(7): 610-616.
5. RCPCH (Royal College of Paediatrics and Child Health), Medicines for children 2003.
6. Vuyk J, Lim T et al. The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology 1995; 83: 8-22.

- **Updated Recommendation**

The Rapporteur proposes the following rewording of the indications: alfentanil is indicated for use as:

- An anesthetic induction agent

- A narcotic analgesic in association with general or regional anesthesia or for painful procedures.
- An analgesic for patients in intensive care on assisted ventilation.

Regarding the dosage:

- Dose recommendations should be proposed by the Applicant for the infants younger than 3 months (based on the studies and on the pharmacokinetic data).

- The maintenance infusion dose of alfentanil in children should remain 1microg/kg/min and not increased to 1-2 microg/kg/min, as there are not enough data to support this dose increase. The dose of 1 microg/kg/min of alfentanil was demonstrated by Ganidagli et al (2003) to be an effective and safe analgesic in anesthesia for children undergoing abdominal surgery.

- Pharmacokinetic information should be added for infants and children for all age groups (in section 5.2 of the SPC).

- The Applicant should address the need of myorelaxants in the youngest aged group as well as the need for assisted ventilation for all indications.

Additional information should come in section 4.2: “In children between 3 and 17 years the dose might need to be higher due to shorter half-life. In infants, neonates and premature babies, the dose should be reduced taking into account the prolonged half-life in these age categories” (see table from Dalens and Veyckemans, 2006).

Regarding the section about pregnancy and lactation:

The Rapporteur proposes the following rewording: “IV administration during childbirth (including Caesarean section) is not recommended, because Rapifen® crosses the placenta and because the fetal respiratory rate is particularly sensitive to opioids. If Rapifen® is administered nevertheless, there should be done only if artificial ventilation can be applied immediately. The use of antidotes is recommended; if the half-life of antidote is shorter than the half-life of alfentanil, repeated administration of the antidote has to be considered”.

Additional remark from the Rapporteur on breastfeeding: it is not needed to wait 24 hours for resuming breastfeeding, because alfentanil has a half-life of 1.3 hours in adults. To wait 10 hours (i.e. about 7 half-lives) is definitively sufficient.

Concrete proposals for the PIL will follow adoption of the definitive text for the SPC. The Applicant should propose a new version of the PIL which takes all SPC remarks into account.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

VI.1 About the indications

In the SPC of the reference product Rapifen®, the second indication has been reworded as follows: alfentanil is used as a “narcotic analgesic **in association with** general or regional anaesthesia or for painful procedures”. The word “adjuvant” has been suppressed according to the request of the rapporteur. This new version of the second indication is endorsed.

About the third indication, it was suggested that alfentanil could be used as “”an analgesic for patients **in intensive care on assisted ventilation**”. The Company has provided a clinical overview on this specific indication. In the Irish SPC of alfentanil, the fourth indication is worded as follows: “for the provision of analgesia and suppression of the respiratory activity in mechanically ventilated patients in intensive care and to provide analgesic cover for painful procedures”. Two clinical studies have been identified by the company to support this indication in children.

Saarenmaa et al (1996)

Randomized, double-blind, controlled study in 10 intubated, mechanically ventilated neonates (2 to 6 days old). The study treatments were placebo and two different doses of alfentanil, 10 and 20 microg/kg intravenously, in random order before 3 tracheal succions (painful procedures). Suction was started 2 minutes post-infusion. At least 6 hours were to elapse between doses. Seven neonates completed the study. Pain relief was only observed with the higher dose of alfentanil (20 microg/kg). After 20 microg/kg alfentanil, a significant reduction of the heart rate increase was observed compared with placebo.
Severe muscle rigidity was registered in 5 of 8 neonates in the 20 microg/kg alfentanil group. Also in the 10 microg/kg group, muscle rigidity was reported in 2 of 9 neonates, while in the placebo group, it was reported in 2 of 8 neonates.

Pokela et al (1992)

20 intubated neonates (age: 6 to 51 years) received alfentanil 9 to 15 microg/kg intravenously prior to various treatment and routine care procedures. Slight and moderate rigidity was observed in 3 to 20 neonates, and in 6 of 20 neonates, respectively. Rigidity was apparent immediately after the injection of alfentanil and prior to beginning the treatment procedure. The rigidity lasted no more than 10 minutes for any neonate, but required increased pressure for manual ventilation and increased inspired O_2 concentrations to treat hypoxemia. However, no major haemodynamic changes were observed. The authors of this study recommended to administer a muscle relaxant in neonates who are treated with alfentanil.

The Applicant reported three older references (1987, 1988) with older children (adolescents) who received alfentanil in bolus doses of infusion. No new information can be found in these publications (for details, please see the Clinical Overview on the use of alfentanil for analgesia in ventilated pediatric patients in intensive care).

In summary, the Applicant considers that these data do not support the use of alfentanil in pediatric patients in the Intensive Care Unit. Therefore, the indication “as analgesic for pediatric patients in intensive care on assisted ventilation” is not accepted. This statement is endorsed by the Rapporteur.

VI.2 About dosage in function of age

The following proposals were made by the Rapporteur:

- Dose recommendations should be proposed by the Applicant for the infants younger than 3 months (based on the studies and on the pharmacokinetic data).

- The maintenance infusion dose of alfentanil in children should remain 1microg/kg/min and not increased to 1-2 microg/kg/min, as there are not enough data to support this dose increase. The dose of 1 microg/kg/min of alfentanil was demonstrated by Ganidagli et al (2003) to be an effective and safe analgesic in anesthesia for children undergoing abdominal surgery.

- Pharmacokinetic information should be added for infants and children for all age groups (in section 5.2 of the SPC).

- The Applicant should address the need of myorelaxants in the youngest aged group as well as the need for assisted ventilation for all indications.

Additional information should come in section 4.2: “In children between 3 and 17 years the dose might need to be higher due to shorter half-life. In infants, neonates and premature babies, the dose should be reduced taking into account the prolonged half-life in these age categories” (see table from Dalens and Veyckemans, 2006).

The Applicant has answered these different issues.

1. There are very few studies that included children aged **1 to 3 months**, therefore the Applicant considers that it would be very difficult to make clear dosage recommendations for this age group. Moreover, the assisted ventilation equipment should always be available even for short procedures due to the higher risk of respiratory depression in neonates. This point has been added in the SPC under section 4.2.

2. The Company is intended to hold a **maintenance infusion dose** of 0.5 to 2 microg/kg/min alfentanil in children. With respect to this dose recommendation, the Applicant mentions the study of Ganidagli (2003), who used a starting infusion dose of 1 microg/kg/min alfentanil. In 42% of patients the dose was titrated upwards because of signs of light (inadequate) anaesthesia and in 34% of patients the dose was titrated downwards. Overall, this gave a weighed mean dose of 1.38 ± 0.43 microg/kg/min, which is consistent with the dose range of 0.5 microg/kg/min in light anaesthesia, to 2 microg/kg/min where the opioid was the primary anaesthetic agent.

3. Regarding the **pharmacokinetic data**, the Company does not believe that it is possible to make dosing recommendations based on PK/PD modeling. However, the new pharmacokinetic data presented by the Rapporteur will be included in section 5.2 of the SPC. A specific table is also added, according to the book of Dalens & Veyckemans, 2006). The Applicant also agreed to include a specific dose recommendation in section 4.2 according to the differences in half-life following the age group: “In children between 3 and 17 years the dose might need to be higher due to shorter half-life. In infants, neonates and premature babies, the dose should be reduced taking into account the prolonged half-life in these age categories”.

4. The Applicant will include in section 4.2 of the SPC the need to use **muscle relaxants** when alfentanil is administered to paediatric patients. This new information is of utmost importance when reviewing the high frequency of muscle rigidity as reported in the two paediatric studies mentioned here above.

The dosage recommendations proposed by the Applicant
(i.e. 0.5 to 2 microg/kg/min as maintenance infusion dose) are endorsed, because adequate information has been added on the two following points:

the need to adapt the dose between the different age groups, in keeping with the (big) differences in half-life in these groups;

-the risk of muscle rigidity and the need to administer preventive muscle relaxants when (higher) doses of alfentanil are used.

VI.3 About pregnancy and lactation

The new wording of information regarding **pregnancy** is endorsed: “Intravenous administration during childbirth (including caesarean section) is not recommended because Rapifen® crosses the placenta and because the foetal respiratory centre is particularly sensitive to opioids. If Rapifen is administered nevertheless, assisted ventilation must be immediately available for use if required. An opioid antagonist for the child must always be available. The half-life of the opioid antagonist may be shorter than the half-life of alfentanil, repeated administration of the opioid antagonist must be considered”.

The Rapporteur had considered that it was not needed to wait 24 hours for resuming **breastfeeding**, because alfentanil has a half-life of 1.3 hours in adults. The Company is not ready to modify this rather conservative approach due to a lack of data. The Rapporteur still believes that there is no scientific reason to extend the “waiting” time to resume breastfeeding beyond 5 half-lives of alfentanil, thus beyond 10 hours. Moreover, the oral bioavailability of alfentanil ingested through breast milk is expected to be low. The Rapporteur estimates the MAH should modify the SmPC.

1. Ganidagli S, Cengiz M et al. Remifentanil vs alfentanil in the total intravenous anaesthesia for paediatric abdominal surgery. Paediatr Anaesth 2003; 13: 695-700.
2. Lactmed – Toxnet 2011 (via Internet).
3. Pokela Ml, Ryhänen PT et al. Alfentanil-induced rigidity in newborn infants. Anesth Analg 1992; 75: 252-257.
4. RCPCH (Royal College of Paediatrics and Child Health), Medicines for children 2003.
5. Saarenmaa E, Huttunen P et al. Alfentanil as procedural pain relief in newborn infants. Arch Dis Child 1996; 75: F103-107.

VII. OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

The suggested changes to the SPC of Alfentanil are endorsed but some additional changes are made after consultation of MSs and MAH:

- In section 4.1, the word “painful” has been removed of the pediatric indication since may suggest “more painful than normal surgical procedure”

- The text suggested for section 4.8 on the risk of muscle rigidity and then reformulated by the MAH has been included.

Recommendation

The MAH is requested to submit a Type IB variation to update the SmPC and PL within 60 days of the date of this report.

Changes in SPC for alfentanil and SPC are listed below. PL should be changed accordingly.

Section 4.1

The proposed indication is shown below:

RAPIFEN is indicated for use in adults as:

- *an anaesthetic induction agent*
- *a narcotic analgesic in general as well as an adjuvant to regional anaesthesia and for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures*

Because of its rapid and short-lasting action, RAPIFEN is particularly suited as a narcotic analgesic for short procedures and outpatient surgery, but also as an analgesic supplement for procedures of medium and long duration, since periods of very painful stimuli can easily be overcome by small increments of RAPIFEN or by adapting its infusion rate.

Additional note from the MAH:
Please note that the SmPC text proposed is only an illustration of the changes that would need to be applied if all national EU SmPCs followed the CCDS text exactly. In many cases it is not the reality that a country's SmPC follows the CCDS text exactly. The Company fully intends to implement the wording agreed in this paediatric workshare procedure as accurately as possible. However, our different national affiliates will need to think carefully when applying the outcome of this procedure, about whether all text is applicable and appropriate for their SmPC.

In countries where applicable text is currently included, it is the intention to delete from the adult indication, the information that bolus injections are for short surgical procedures and bolus injection, supplemented by increments or by infusion, are for long surgical procedures. The Company does not consider this change to the adult indication wording as being a material change. The reason for this proposed change is to avoid duplication of information, since it has been agreed during this paediatric procedure that the following text will be added to section 4.2 of the SmPCs:

"RAPIFEN should be used as bolus injections (short procedures) or bolus supplemented by increments or by infusion (long painful surgical procedures)."

Rapporteur's comment: Following comments that the adult indication is outside the scope of this paediatric WS procedure the applicant is encouraged to propose an updated of the adult indication, according to what has been discussed in this procedure, with the next clinical updated of the SmPC submitted at national level. The update of the adult indication will not be included in the IB variation to be submitted as a consequence of this WS.

RAPIFEN is indicated for use in neonates, infants, and children as:

- An opioid in association with a hypnotic to induce anaesthesia
- a narcotic analgesic in association with general anaesthesia, and for both short and long surgical procedures

Section 4.2

RAPIFEN should be used as bolus injections (short procedures) or bolus supplemented by increments or by infusion (long painful surgical procedures).

The dosage of RAPIFEN should be individualized according to age, body weight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.

The initial dose should be reduced in the elderly and in debilitated patients. ~~In children it should be increased. The effect of the initial dose should be taken into account in determining supplemental doses……~~

Adults

….

Paediatric patients

Assisted ventilation equipment should be available for use in children of all ages even for short procedures in spontaneously breathing children.

Data in children, particularly those aged 1 month to 1 year are limited (see section 5.2).

Neonates (0-27 days): The pharmacokinetics are very variable in neonates, particularly in those born preterm. Clearance and protein binding are lower, and a lower dose of alfentanil may be required. Neonates should be closely monitored and the dose of alfentanil titrated according to the response.

Infants and toddlers (28 days to 23 months): Clearance may be higher in infants and toddlers compared to that in adults. For maintenance of analgesia, the rate of infusion of alfentanil may need to be increased.

Children (2 to 11 years): Clearance may be slightly higher in children and the rate of infusion may need to be increased.

Adolescents: The pharmacokinetics of alfentanil in adolescents are similar to those in adults and no specific dosing recommendations are required.

Dosing recommendations for paediatric patients

The wide variability in response to alfentanil make it difficult to provide dosing recommendations for younger children. For older children a bolus dose of 10 to 20 µg/kg alfentanil for induction of anaesthesia (i.e. to supplement propofol or inhalation anaesthesia) or as an analgesic is considered appropriate. Supplemental boluses of 5 to 10 µg/kg alfentanil at appropriate intervals can be administered.

To maintain analgesia in children during surgery, a RAPIFEN infusion rate of 0.5 to 2 µg/kg/min may be administered. The dose must be titrated up or down according to the needs of the individual patient. When combined with an intravenous anaesthetic agent the recommended dose is approximately 1 µg/kg/min.

There may be a higher risk of respiratory complications and muscle rigidity when alfentanil is administered to neonates and very young children. Necessary precautions are detailed in section 4.4.

Section 4.4

The SmPCs should be amended to contain warnings and precautions for use that are specific to the pediatric population:

- *Paediatric population*
- There may be a higher risk of respiratory complications when alfentanil is administered to neonates and very young children than when it is used in older children and adults. For this reason, young paediatric subjects should be monitored immediately after administration of alfentanil is commenced. Assisted ventilation equipment should be available for use in children of all ages, even for short procedures in spontaneously breathing children.
- If alfentanil is used in neonates and young infants, the simultaneous use of a muscle relaxant should be considered because of the risk of muscle rigidity. All children should be monitored for a sufficient period of time following cessation of treatment with alfentanil to ensure the return of spontaneous respiration has been achieved
- Due to variable pharmacokinetics in neonates a lower dose of alfentanil may be required. Neonates should be closely monitored and the dose of alfentanil titrated according to the response. (see section 4.2)

Section 4.6

The information below is in the current CCDS:

> *I.V. administration during childbirth (including caesarian section) is not recommended, because RAPIFEN crosses the placenta and because the fetal respiratory centre is particularly sensitive to opiates. If RAPIFEN is administered nevertheless, an antidote for the child should always be at hand.*

The SmPCs will be amended to align with the following text:

> Intravenous administration during childbirth (including caesarian section) is not recommended because RAPIFEN crosses the placenta and because the foetal respiratory centre is particularly sensitive to opioids. If RAPIFEN is administered

nevertheless, assisted ventilation equipment must be immediately available for use if required.

An opioid antagonist for the child must always be available. The half-life of the opioid antagonist may be shorter than the half-life of alfentanil, therefore, repeated administration of the opioid antagonist must be considered.

Section 4.8

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults, with the exception of the following:

Mild to moderate muscle rigidity has been seen frequently in neonates, although the number of neonates included in clinical studies was small. Severe rigidity and jerking can occur less commonly and may be accompanied by transient impaired ventilation, especially with high doses of RAPIFEN or with a rapid rate of intravenous injection.

Section 5.2

The information below in italics is in the current CCDS. This text will be **deleted** from SmPCs:

~~*The plasma clearance in newborns is approximately 7.2 ± 3.2 mL/kg/min and 4.7 ± 1.7 mL/kg/min in children between 4.5 to 7.75 years. The volume of distribution at steady state was 1230 ± 520 mL/kg in newborns and 163.5 ± 110 mL/kg in children. The half-life is 146 ± 57 minutes in newborns and 40.2 ± 8.9 minutes in children.*~~

The following information will be added to SmPCs.

Paediatric population

The data in children are limited. The values for the pharmacokinetic parameters are shown in the table below.

Pharmacokinetic Parameters of Alfentanil in Paediatric Subjects			
	$t_{1/2\beta}$ (hr)	**CL (mL/kg/min)**	**Vd_{ss} (L/kg)**
Preterm Neonates (0-27 days) Gestational age 25-40 weeks; ***n= 68***	0.7-8.8	0.9-8.4	0.3-1.2
Term Neonates (0-27 days) Gestational age: 35-41 weeks; ***n= 18***	4.1-5.5	1.7-3.2	0.5-0.8
Infants & Toddlers 28 days - 23 months; ***n= 34***	0.9-1.2	7.7-13.1	0.4-1.1
Children 2-11 years; ***n= 32***	0.7-1.3	4.7-10.2	0.2-1.0
Adolescents 12-14 years; ***n= 3***	1.1-1.9	5.5-7.4	0.3-0.6

Note: Data for neonates, infants, and children are given as range of mean values. CL = clearance, Vd_{ss} = volume of distribution at steady state, $t_{1/2\beta}$ = half-life in the elimination phase.

Protein binding in newborns is 75% and increases in children to 85%.

Pharmacokinetic information on the use of alfentanil in children is limited. Alfentanil is metabolized by CYP3A4. CYP3A4 activity is low in neonates and increases after birth to reach 30 to 40% of adult levels at 1 month of age.

VIII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

EU Country	Marketing Authorisation Holder (MAH)	Product Full Name
Austria	Janssen-Cilag Pharma GmbH - AT	Rapifen 1 mg – Ampullen Rapifen 5 mg - Ampullen
Belgium	Janssen-Cilag NV - BE	Rapifen ampullen
Czech Republic	Janssen-Cilag s.r.o - CZ	Rapifen
Denmark	Janssen-Cilag A/S - DK	Rapifen 0,5 mg/ml injektionsvæske, opløsning
Finland	Janssen-Cilag OY - FI	Rapifen 0,5 mg/ml injektioneste, liuos
France	Janssen-Cilag - FR	Rapifen 1 mg (0,5 mg/ml) Solution Injectable Rapifen 5 mg (0,5 mg/ml) Solution Injectable
Germany	JANSSEN-CILAG GmbH - DE	Rapifen 0,5 mg/ml Injektionslösung
Ireland	Janssen-Cilag Limited - UK	Rapifen 500 micrograms/ml, solution for injection or infusion
Italy	Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A. – IT	Fentalim, 0,5 mg/ml Solution for Injection
Liechtenstein	Janssen-Cilag AG - CH	Rapifen
Luxembourg	Janssen-Cilag NV - BE	Rapifen ampullen
Netherlands	Janssen-Cilag BV - NL	Rapifen oplossing voor injectie 0,5 mg/ml, oplossing voor injectie
Norway	Janssen-Cilag AS - NO	Rapifen 0,5 mg/ml injeksjonsvæske, oppløsning
Portugal	Janssen Farmacêutica Portugal, Lda - PT	Rapifen 1mg/2ml solução injectável Rapifen 5mg/10ml solução injectável
Spain	Janssen-Cilag S.A. - ES	Limifen 0,5 mg/ml solución inyectable
Sweden	Janssen-Cilag AB - SE	Rapifen 0.5 mg/ml injektionsvätska, lösning
UK	Janssen-Cilag Limited - UK	Rapifen (0.5 mg/ml) Rapifen Intensive Care (5 mg/ml)