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

Ketamine

Ketalar

UK/W/0085/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	13 September 2017

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	See section XII
INN (or common name) of the active substance:	Ketamine
MAH:	See section XII
Pharmaco-therapeutic group (ATC Code):	N01AX03
Pharmaceutical form(s) and strength(s):	Pharmaceutical form: Solution for injection or infusion Strengths: 10 mg/ml, 50 mg/ml, 100 mg/ml

I. EXECUTIVE SUMMARY

This is a data submission for ketamine in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. The UK is the rapporteur for this procedure.

Ketamine is a rapid-acting, non-barbiturate, anaesthetic agent for diagnostic and surgical procedures. It is best suited for short procedures, but it can be used with additional doses for longer procedures. Ketamine is also indicated for induction of anaesthesia prior to the administration of other general anaesthetic agents.

One MAH submitted a summary of published literature relevant to the use of ketamine in children. Additionally, the MAH submitted paediatric safety data from their post-marketing database and published literature. The MAH stated that the safety profile of ketamine in paediatric patients is similar to that in the adult population and consistent with the product labelling.

The MAH concluded that the benefit/risk profile of ketamine remains favourable. However, the MAH proposes a new statement in section 4.1 of the Summary of Product Characteristics (SmPC) to clarify the specific age groups in which ketamine is indicated.

The rapporteur agrees that based on the data provided as part of this European paediatric work-sharing procedure under Article 45, the benefit/risk balance of ketamine remains unchanged for the paediatric population. In line with the SmPC guideline 2009, the rapporteur endorses the new statement in section 4.1 to clarify the specific age groups in which ketamine is indicated, whilst it is also acknowledged that consistency will be maintained with posology statements already present in section 4.2.

II. RECOMMENDATION

Based on the review of the submitted paediatric data, a SmPC change is proposed in section 4.1.

Summary of outcome

- ☐ No change
- ☒ Change
  - ☐ New study data
  - ☐ New safety information
  - ☒ Paediatric information clarified: <section 4.1>
  - ☐ New indication

The final SmPC recommendation is presented below:

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.1 Therapeutic indications
[This section should be amended to include the below wording]

Ketamine is indicated in children and in adults.

III. INTRODUCTION

On 23.10.2015, the MAH submitted a summary of published literature relevant to the use of ketamine in children, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

In addition, the following documentation has been included as per the procedural guidance:

- A short critical expert overview

- Results relevant to paediatrics from a search in the MAH post-marketing safety database

IV. SCIENTIFIC DISCUSSION

a. Information on the pharmaceutical formulation used in the clinical studies

Ketamine is a rapid-acting, non-barbiturate, anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. It is best suited for short procedures, but it can be used with additional doses for longer procedures. Ketamine is also indicated for induction of anaesthesia prior to the administration of other general anaesthetic agents.

Specific areas of use have included but are not limited to the following:
1. Debridement and skin grafting in burn patients
2. Neurodiagnostic procedures such as myelogram, and lumbar puncture
3. Diagnostic and operative procedures of the eye, ear, nose and mouth
4. Sigmoidoscopy and minor rectal surgery
5. Cardiac catheterization procedures
6. Orthopaedic procedures

Ketamine induces sedation, immobility, amnesia, and marked analgesia. The anaesthetic state produced by ketamine has been termed “dissociative anaesthesia” in that it appears to selectively interrupt association pathways of the brain before producing somesthetic blockade. It may selectively depress the thalamoneocortical system before significantly obtunding the reticular-activating and limbic systems. Numerous theories have been proposed to explain the effects of ketamine, including binding to N-methyl-D-aspartate (NMDA) receptors in the central nervous system, interactions with opiate receptors at central and spinal sites, and interaction with norepinephrine, serotonin, and muscarinic cholinergic receptors. The activity on NMDA receptors may be responsible for the analgesic as well as psychiatric (psychotic) effects of ketamine.
Ketamine has sympathomimetic activity resulting in tachycardia, hypertension, increased myocardial and cerebral oxygen consumption, increased cerebral blood flow, and increased intracranial and intraocular pressure. Ketamine is also a potent bronchodilator.
Clinical effects observed following ketamine administration include increased blood pressure, increased muscle tone (may resemble catatonia), opening of eyes (usually accompanied by nystagmus), and increased myocardial oxygen consumption.

Ketamine is marketed in 20 countries and is on the World Health Organization Model Lists of Essential Medicines.

Current UK SmPC text relevant to the use of ketamine in children

4.1 Therapeutic indications

Ketalar is recommended:

As an anaesthetic agent for diagnostic and surgical procedures. When used by intravenous or intramuscular injection, Ketalar is best suited for short procedures. With additional doses, or by intravenous infusion, Ketalar can be used for longer procedures. If skeletal muscle relaxation is desired, a muscle relaxant should be used and respiration should be supported.

For the induction of anaesthesia prior to the administration of other general anaesthetic agents.

To supplement other anaesthetic agents.

Specific areas of application or types of procedures:

When the intramuscular route of administration is preferred.

Debridement, painful dressings, and skin grafting in burned patients, as well as other superficial surgical procedures.

Neurodiagnostic procedures such as pneumoencephalograms, ventriculograms, myelograms, and lumbar punctures.

Diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions. Note: Eye movements may persist during ophthalmological procedures.

Anaesthesia in poor-risk patients with depression of vital functions or where depression of vital functions must be avoided, if at all possible.

Orthopaedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies.

Sigmoidoscopy and minor surgery of the anus and rectum, circumcision and pilonidal sinus.

Cardiac catheterization procedures.

Caesarian section; as an induction agent in the absence of elevated blood pressure.

Anaesthesia in the asthmatic patient, either to minimise the risks of an attack of bronchospasm developing, or in the presence of bronchospasm where anaesthesia cannot be delayed.

4.2 Posology and method of administration

Adults, elderly (over 65 years) and children:

As with all general anaesthetics, the individual response to Ketalar varies according to a number of factors including dose, route of injection and body weight of the patient so dosage recommendations cannot be absolutely fixed. The dose should be titrated against the patient's requirements.

KETALAR AS THE SOLE ANAESTHETIC AGENT

Intravenous infusion

General Anaesthesia Induction

An infusion corresponding to 0.5 – 2 mg/kg as total induction dose.

Maintenance of anaesthesia

Anaesthesia may be maintained using a microdrip infusion of 10 - 45 microgram/kg/min. The rate of infusion will depend on the patient's reaction and response to anaesthesia. The dosage required may be reduced when a long acting neuromuscular blocking agent is used.

Intramuscular Route

The initial dose of Ketalar administered intramuscularly may range from 6.5 mg/kg to 13 mg/kg (in terms of ketamine base). A low initial intramuscular dose of 4 mg/kg has been used in diagnostic manoeuvres and procedures not involving intensely painful stimuli. A dose of 10 mg/kg will usually produce 12 to 25 minutes of surgical anaesthesia.

Intermittent Injection

Intravenous Route

The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5mg/kg (in terms of ketamine base). The average amount required to produce 5 to 10 minutes of surgical anaesthesia has been 2.0 mg/kg. It is recommended that intravenous administration be accomplished slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

- **The MAH's statements and previous communications regarding ketamine paediatric information**

Ketamine is widely used in children (WHO recommended anaesthetic) and clinical experience has shown it to be a relatively safe and effective anaesthetic in children. When the product was first authorised over 40 years ago, the original marketing authorisation application included clinical data demonstrating successful anaesthesia in both paediatric and geriatric populations. The original SmPC therefore made reference to a 'variable' aged population and this was implicitly understood to include 'children' as well as adults.

Compared to the current SmPC in the UK, the early SmPC contained similar information in the dosage section. The following text is an extract from the original approved SmPC in 1973:

> *"As with other general anaesthetic agents, the individual response to Ketalar is somewhat varied depending on the dose, route of administration, age of patients and concomitant use of other agents, so that dosage recommendation cannot be absolutely fixed. The dose should be titrated against the patient's requirements."*

In response to the requirements of National UK legislation, the 1983 renewal for Ketalar 10 mg/ml product in the UK included a Clinical Overview of the literature, to support the continued use of the product in adults and children although the terminology used in the SmPC was not updated specifically to mention children at that time.

In 1988, a variation was submitted to add Intravenous (IV) infusion as an alternative method of administration and the UK variation template at that time stated that the applicant should 'distinguish between adults, children and the elderly and between different clinical indications'. Consequently the phrase ''Adults, elderly (over 65 years) and children', was added to the posology section of the SmPC in September 1988.

In 2014, during the renewal of marketing authorisation for Ketalar, the MAH was requested to add specific dosage regimens for the paediatric population to the product label. The MAH conducted a review of literature related to the use of ketamine in patients less than 18 years of age. The results of this review demonstrated that pharmacokinetic parameters (elimination half-life=$t_{1/2}$, volume distribution at steady state=Vss, and clearance=CL) in the literature reported following IV administration of racemic ketamine appear similar between adults and children. Based on the information available as well as the extensive clinical experience, ketamine is dosed in paediatric patients according to body weight, as it is in adults. There is no lower age limit for administration. Furthermore, in all patients, response to general anaesthetic agents should be individualised and titrated to the patient's requirements.

Rapporteur's comments:

The rapporteur endorses the dosing in paediatric patients to be on a mg/kg basis. Additionally, it is supported that response to general anaesthetic agents should be individualised and titrated to the patient's requirements.

b. Non-clinical aspects

No MAH non-clinical studies relevant to the paediatric use of ketamine were conducted.
The MAH reported that non-clinical literature data have shown that ketamine can induce NMDA antagonist-induced neuronal cell death in juvenile animals (apoptosis) when administered in high doses or for prolonged periods. Observations have been made in mice, rats and monkeys. However, the relevance of this finding to human use is unknown.

Rapporteur's comments:
No significant conclusions of clinical significance can be drawn from the above non-clinical information.
The MAH has also presented a review and several publications regarding the clinical perspectives of ketamine and neurotoxicity, which are further detailed in section V of the report. These articles do not provide sound evidence of an association between adverse neurodevelopmental/neurotoxicity outcomes and the use of ketamine for paediatric anaesthesia.

With regards to non-clinical data, the current UK SmPC of ketamine states that:

> *5.3 Preclinical safety data*
> Preclinical safety data does not add anything of further significance to the prescriber.

The rapporteur considers that no changes are warranted to section 5.3 of the SmPC based on the non-clinical information submitted within this paediatric work-sharing procedure.

It is noted that in December 2016, the US FDA published a Drug Safety Communication detailing changes to the US product information for general anaesthetics and sedation medicines to warn against repeated or prolonged use in young children or in pregnant women during their third trimester, as this may affect the development of children's brains.
The FDA communication can be found here:
http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm
This advice is based on studies in animals and in children, some of which have suggested that these medicines may have negative effects on children's learning or behaviour. FDA further clarified that more research is still needed to provide additional information about the safe use of these medicines in young children and pregnant women.

c. Clinical aspects

There have been no MAH-sponsored clinical studies of ketamine use in patients under 18 years of age.

For the purpose of this Article 45 work-sharing procedure, the MAH has provided a review of published literature on ketamine and completed a search of the MAH post-marketing safety database. Information on the use of ketamine in children from published literature is summarised below.

- **Pharmacokinetics of ketamine**

Absorption, Distribution, Metabolism, and Elimination
Ketamine is rapidly absorbed following parenteral administration. Ketamine readily crosses the placenta and is rapidly distributed into highly perfused tissues (e.g. heart, lung, and brain),

followed by muscle and peripheral tissues, and then fat.[1,2] The distribution phase lasts about 45 minutes, with a half-life of 10 to 15 minutes, which corresponds clinically to the anaesthetic effect of the drug.[1,2] Peak plasma levels averaged about 0.75 µg/mL and CSF levels were about 0.2µg/mL, one hour after dosing.
Ketamine undergoes hepatic N-demethylation (via the cytochrome P450 system) and hydroxylation of the cyclohexanone ring, with the formation of water-soluble conjugates which are excreted in the urine.[1,2] Further oxidation also occurs with the formation of a cyclohexanone derivative. The unconjugated N-demethylated metabolite was found to be less than one sixth as potent as ketamine. The unconjugated demethyl cyclohexanone derivative was found to be less than one tenth as potent as ketamine.
Studies in human subjects resulted in the mean recovery of 91% of the dose in the urine and 3% in the faeces.

There is limited published PK data of racemic ketamine in children. The pharmacokinetic parameters following intravenous (IV) administration of racemic ketamine in children and adults appear to be similar (Table 1).

Table 1. Published pharmacokinetic data of IV administration of racemic ketamine in adults and children

Author	Dose (mg/kg)	Age[a] in years	$t_{½}$ (min)	V_{ss} (L/kg)	CL (mL/min/kg)
Pharmacokinetic Parameters Reported in Literature for Adults					
Clements[3]	0.125[b]	33.8	180	2.1	16
	0.25[b]	33.8	180	3.1	19
Domino[4]	2.0-2.2[b]	45.3 (31-57)	158	NA	NA
Domino[5]	2.2[b]	32.3 (26-41)	135	1.8	14
Grant[6]	2.0[b]	52 (37-76)	153	2.3	13
Wieber[7]	2.5[b]	NA	151	NA	NA
Yanagihara[8]	20mg[b]	NA (27-40)	122	2.5	19
Pharmacokinetic Parameters Reported in Literature for Children					
Grant[6]	2.0[b]	6.1 (5-9)	100	1.9	17
Malinovsky[9]	3.0[b]	4.8 (2-8)	125	2.8	22

a: Age: Mean (range)
b: Administered IV as a bolus dose.
$t_{½}$=elimination half-life; Vss=volume of distribution at steady state; CL=clearance; NA=Data are not available.

There are no published data of PK parameters of ketamine in children following IM administration. Therefore, PK parameter comparisons of IM ketamine between adults and children have not been made.

- **Efficacy**

No designated paediatric studies were conducted during the clinical development of ketamine. The clinical development program was conducted in adults and was considered adequate at that time to assess the efficacy of ketamine in relevant clinical settings. Since the time of initial market authorization, numerous reviews and clinical studies in both adults and children have been published on the use of ketamine for analgesia, anaesthesia, and other indications.

Literature clinical data

A comprehensive literature search for ketamine was performed in MEDLINE, EMBASE, and BIOSIS [Dated: 14 August 2015 in all 3 databases] to identify scientific literature articles, systemic reviews, meta-analysis, and guidelines discussing the use and benefits of ketamine in the paediatric population. In addition, guidelines and cited literature from Cochrane systemic reviews were screened to identify supporting information not available in the aforementioned literature databases.

The submitted publications are presented by the indication of use.

i. Anaesthesia

A review article by **Bergman** evaluated the pharmacology and use of racemic ketamine in paediatric anaesthesia.[10] The paediatric sedation protocols that were reviewed included doses of 3 mg/kg IM and 1-2 mg/kg IV. Bergman concluded that ketamine is safe and effective for use as an anaesthetic and sedative in paediatric patients.

Moawad et al[11] conducted a randomised double-blind study to evaluate the efficacy of ketamine in the prevention of emergence agitation (EA) after sevoflurane general anaesthesia in 120 children aged between 2 and 7 years undergoing MRI scan. The patients were randomly distributed into 3 groups of 40 each to either receive normal saline, 0.25 mg/kg ketamine IV 10 minutes prior to the end of the procedure (n = 40), or 1.0 mg/kg of ketamine IV before sevoflurane induction. The EA score was assessed using paediatric anaesthesia emergence delirium (PEAD) scale. A significantly lower EA score was reported in ketamine 1.0 group compared to ketamine 0.25 and saline groups (2.50 ± 0.99 vs. 4.63 ± 0.95 and 12.00 ± 1.59 respectively, $p<0.05$). Further, Ketamine 0.25 group showed significantly lower EA score in comparison with saline group (4.63 ± 0.95 vs. 12.00 ± 1.59, $p<0.05$). Patients in ketamine 1.0 group reported significantly lower incidence of pausing and interruption of MRI procedure in comparison with ketamine 0.25 and saline groups (2.5% vs. 15% and 17.5% respectively, $p<0.05$). No significant differences as regards nausea, vomiting, desaturation, scan and discharge times among the studied groups ($p>0.05$) were found. The authors therefore concluded that the premedication with ketamine was effective in reducing EA without delay in recovery and significantly reduced the frequency of pausing of MRI scan.

Thomas et al[12] conducted a double-blind randomised study to evaluate the efficacy of IV ketamine and varying doses of IV fentanyl on postoperative EA in 114 children aged between 2 and 10 years receiving sevoflurane anaesthesia. The children were undergoing herniotomy under sevoflurane anaesthesia. The patients were randomly divided into 3 groups, namely, Group A receiving ketamine 0.5 mg/kg, Group B fentanyl 2 µg/kg and Group C fentanyl 3 µg/kg at the time of induction. Postoperative EA was assessed every 5 minutes during first 60 minutes of post-anaesthesia care unit (PACU) stay using Aono's four point scale. A significantly less mean duration of PACU stay was observed in Group C compared to Group A ($P = 0.032$). The number of children who developed EA in group B was significantly higher in Group B compared to Group A ($P=0.003$) and Group C ($P=0.001$) (65.8% vs. 31.6% and 28.9% respectively). The necessity of rescue medication after EA was significantly higher in Group B compared to Group A and C (65.8% vs. 31.6% and 28.9% respectively, $p<0.001$). Duration of anaesthesia with EA was less in Group B compared to A and C (67.08 ± 25.13 vs. 80.42 ± 31.51 and 82.09±31.11 respectively). Time to extubation with EA was reported to be higher in Group C compared to Group A and B (9.09±2.21 vs. 7.58±2.47 and 7.44±2.75 respectively). Time to consciousness with EA was statistically similar between the 3 treatment groups. Duration of PACU stay with EA was higher in Group A compared to Group B and C (83.33 ± 5.37 vs. 77.2 ± 6.14 and 76.36 ± 8.97 respectively). The authors therefore concluded that ketamine 0.5 mg/kg IV or fentanyl 3 µg/kg IV administered at the time of induction reduced the incidence of EA in comparison to fentanyl 2 µg/kg, without delaying recovery.

Bonneau et al[13] evaluated the efficacy of ketamine as an anaesthetic for invasive procedure in paediatric oncology. Ketamine was administered IV in 48 patients with an average age of 7.4 years and who underwent 115 procedures. Pain was assessed using Face, Legs, Activity, Cry, Consolability (FLACC) scale. Pain was reported to be under control during and after the procedure (89.5% FLACC <4/10 during and 96.6% FLACC/EVA <4/10 after). The authors therefore

concluded that ketamine could be used as an alternative to general anaesthesia for invasive procedures in paediatric oncology.

Tamminga et al[14] conducted a double-blind randomised study in 16 children with acute lymphoblastic leukaemia (ALL) aged between 4 and 16 years. IV Ketamine (1.0 - 1.5 mg/kg) was administered immediately before bone marrow punctures (BMPs). Patients were randomised either to receive diazepam or placebo. Pain was assessed on a 100-point scale using the Oucher method. The patients were interviewed 45 minutes after completion of the procedure. A questionnaire was sent to the child and the parents 1 week after the second BMP to evaluate which procedure they preferred and why. The pain scores were low, immediately after awakening from the ketamine anaesthesia (0 in 20 of the 32 procedures, 10 in 3, 20 in 2, and 30 in 2 others). No pain score was obtained from 5 procedures as either the patient was too sleepy or too young. Another dose of IV ketamine (0.3 - 0.5 mg/kg) was required during 8 procedures (with diazepam: 5 procedures, with placebo: 3 procedures) to avoid the child awakening before the completion of procedure. Sudden awakening was reported by 6 children after placebo and by 1 child after diazepam premedication. The most frequently occurred side effects are diplopia (31), dry mouth (24), irritability (18) and hypersalivation (14). No statistical significant differences on vital signs or adverse events were found between the 16 ketamine anaesthesia with and those without diazepam premedication. The authors therefore concluded that ketamine anaesthesia appeared as effective after diazepam premedication as after placebo premedication.

Irving et al[15] conducted a study to assess the efficacy of anaesthesia technique performed for burns in 72 children aged between 7 and 130 months. The children were undergoing anaesthesia for desloughing and skin grafting. The anaesthesia technique involved administration of trimeprazine 3 mg/kg, droperidol 0.2 mg/kg and atropine 0.02 mg/kg as premedication followed by ketamine 10 mg/kg IM plus nitrous oxide 66% in oxygen administered via nasal prongs at 350 mL/kg/minute. Supplementation with additional IV ketamine as a continuous infusion at 2-4 mg/kg/hour, or as 1 mg/kg boluses, was administered as required. Later induction with halothane was given to the patient. Postoperative analgesia was observed to be excellent in 92% of children. Only 2 of the 17 children received paracetamol (10-15 mg/kg) for pain. No additional clinical benefits were observed with fentanyl plus ketamine, compared to ketamine alone.

Begec et al[16] conducted a study to compare the effects of ketamine and alfentanil administered before induction of anaesthesia with propofol, on the hemodynamic changes and ProSeal laryngeal mask airway (PLMA) insertion conditions in 80 children aged between 3 and 132 months. Patients were randomly allocated to receive either IV alfentanil 20 µg/kg or IV ketamine 0.5 mg/kg administered over 30 seconds. Following administration of the study agents, propofol 4 mg/kg was administered over 10 seconds. The pain on injection of propofol was graded using a four point scale. Changes in mean arterial pressure (MAP), heart rate (HR), and peripheral capillary oxygen saturation (SpO2) following induction were recorded. There was a significant increase in heart rate in the ketamine group compared with the alfentanil group ($p<0.05$). When compared to the ketamine group, patients on alfentanil showed decreased MAP ($p<0.05$). Results indicated that mixing ketamine with propofol showed a success rate of 100% as compared to mixing alfentanil with propofol which achieved a success rate of 95%. The authors therefore concluded that the administration of ketamine with propofol, preserved hemodynamic stability and reduced the time to the return of spontaneous breathing during PLMA placement.

Espahbodi et al[17] conducted a randomised clinical study to compare the efficacy of ketamine with atropine as a chronotropic anticholinergic drug in 90 patients aged between 4 and 10 years and to evaluate which one could better prevent oculocardiac reflex (OCR). The patients were randomised to 3 groups namely Group K (which received ketamine), Group A (which received IV injection of atropine) and Group C (the placebo group). Induction of general anaesthesia was done in the patients as follows: group K (ketamine, 1.5 mg/kg, fentanyl, 1 µg/kg, and atracurium, 0.5

mg/kg); group C as control group (propofol, 2 mg/kg, fentanyl, 1 µg/kg, and atracurium, 0.5 mg/kg), and group A (atropine, 0.15 mg/kg, propofol, 2 mg/kg, fentanyl, 1 µg/kg, and atracurium 0.5 mg/kg). Results indicated that the incidence of OCR was 20% in the ketamine group, 63% in the control group and 43% in the atropine group. The authors therefore concluded that as ketamine was associated with a lower incidence of the OCR, it may be the better choice as an induction drug for eye surgery.

Mizrak et al[18] conducted a study to compare the efficacy of IV ketamine with propofol anaesthesia in 60 children aged between 4 and 11 years undergoing strabismus surgery. The patients were assigned to 2 groups namely Group ketamine (Group K, n=30) and Group propofol (Group P, n=30); and ketamine (1–3 mg/kg/hour) and propofol (6–9 mg/kg/hour) were administered to the respective groups following fentanyl 1 µg/kg infusion. The RT, postoperative agitation score for behaviour over a scale of 1-5, face pain scale (FPS) over a scale of 0-10 and Ramsay sedation score (RSS) over numerical scale of 1-6 were assessed to evaluate the postoperative pain. Results indicated that the recovery time in Group K was lesser than that in Group P (P = 0.008). In Group K, the post-operative agitation score was significantly lower than in Group P (P =0.005). The FPS in Group K was considerably lower than that in Group P (P =0.001) post-surgery at 60th minute (p=0.02) and during awakening (P=0.01), and the RSS was higher in Group K than in Group P. The author concluded that the infusion of ketamine with fentanyl gave better anaesthesia than propofol in children undergoing strabismus surgery.

Hannallah[19] sought to determine whether low dose IM ketamine (2 mg/kg) would facilitate inhaled induction of anaesthesia in children who are uncooperative. Thirty-five children were anesthetised with halothane and nitrous oxide for insertion of tympanotomy tubes. Twenty (20) of those children were deemed by the anaesthesiologist to be uncooperative and received 2 mg/kg of IM ketamine prior to induction of anaesthesia. The onset time (time from ketamine administration until induction of inhaled anaesthesia could be started) was 2.7 ± 0.3 min. The quality of the subsequent acceptance of inhaled induction with halothane was excellent in 61% of the patients and adequate in the remaining 39%. The recovery and discharge times were compared with those observed in 15 matched children who accepted induction of anaesthesia via a mask without the use of ketamine. Recovery time was not prolonged, but home discharge was delayed by an average of 13 min in the ketamine group ($p<0.04$). Neither emergency nor post anaesthetic reactions were observed. There were no incidents of any behavioural changes or psychological disturbances that were observed by parents within 24 hours after surgery. The authors therefore concluded that low-dose IM ketamine was an acceptable pre-induction drug, in difficult paediatric patients who were uncooperative during other methods of induction such as inhaled induction of anaesthesia.

Tomatir et al[20] conducted a randomised study to investigate the effects of low dose ketamine before induction on propofol anaesthesia in 43 children aged between 9 days and 7 years, undergoing MRI. The children with ASA physical status 1 or 2, undergoing elective MRI were randomly assigned to receive IV either a 2.5 mg/kg bolus of propofol in 30 seconds followed by an infusion of 100 µg/kg/min (n=20), or a 1.5 mg/kg bolus of propofol in 30 seconds immediately after a 0.5 mg/kg rapid bolus of ketamine followed by an infusion of 75 µg/kg/min (n=23). If a child moved during the imaging sequence, a 0.5-1 mg/kg top up boluses of propofol was given. Parameters assessed and recorded included systolic and diastolic blood pressures, HR, peripheral oxygen saturation and respiratory rates, apnoea, the requirement for airway opening manoeuvres, secretions, nausea, vomiting, and movement during the imaging sequence and recovery times. Peripheral oxygen saturation and respiratory rate were similar in both the groups. Apnoea associated with desaturation was observed in 3 patients of the propofol group; whereas, those in propofol-ketamine group were apnoea free (difference between the groups was not significant). One of these patients was treated using tactile stimulus; while, the other 2 patients required chin lift and airway placement. Further, 2 patients in propofol-ketamine group required chin lift and airway placement because of airway obstruction associated with a decrease of

respiratory rate. Systolic pressures decreased significantly in propofol group (P = 0.0001) after propofol administration while they remained stable in propofol-ketamine group. In the propofol group diastolic pressure decreased starting from the first minute and returned to initial values in the tenth min (P=0.00034) while no changes were observed in group propofol-ketamine group (p>0.05). Heart rate decreased significantly in both the groups following propofol or propofol-ketamine administration (p<0.05). The 2 groups were similar with respect to requirements for airway opening manoeuvres, secretions, nausea-vomiting, and movement during the imaging sequence, and recovery time. The authors therefore concluded that IV administration of low dose ketamine prior to propofol induction and infusion can decrease adverse hemodynamic effects commonly encountered when using propofol alone, without changing recovery time and quality in children undergoing MRI. Further studies are warranted to determine the optimum infusion rate of propofol with co-administration of ketamine for preventing movement in different age groups in children.

Rapporteur's comments:
The review article by **Bergman**[10] does not specify the age range of patients and number of patients that were included in the study. Limited information on the characteristics of the paediatric study population precludes robust conclusions to be made on efficacy and safety from this article.

Moawad et al[11] and **Thomas et al**[12] reported that premedication with ketamine can reduce emergence agitation in children aged 2 to 10 years who received sevoflurane anaesthesia and there was no delay in recovery. Nonetheless, as advised in the SmPC of ketamine, patients in recovery should be observed including monitoring of their vital signs. If, during the recovery, the patients show any indication of emergence delirium, consideration may be given to the use of diazepam or thiobarbiturate for severe emergence reactions.

Bonneau et al[13] reported the possibility of using ketamine as an alternative to general anaesthesia in invasive procedures in paediatric oncology. Indeed, ketamine is recognised as a hypnotic agent, providing obtundation and loss of consciousness and it is also an analgesic agent. It can act as a sole IV agent to provide general anaesthesia in various diagnostic and surgical procedures.[62]

Tamming et al[14] concluded that ketamine anaesthesia appeared as effective after diazepam premedication as after placebo premedication. The rapporteur notes that diazepam premedication might be beneficial as ketamine produces disturbing post-anaesthetic dreams and hallucinations. These can occur at the time of emergence from anaesthesia and for several weeks. In adults, the incidence of this effect is 30-50%; in pre-pubertal children, it may be 5-10%. Premedication with a benzodiazepine greatly reduces these sequelae and a benzodiazepine is routinely considered for children receiving ketamine anaesthesia.[62]

Espahbodi et al[17] concluded that as ketamine was associated with a lower incidence of the oculocardiac reflex, it may be the better choice as an induction drug for eye surgery. **Mizrak et al**[18] concluded that the infusion of ketamine with fentanyl gave better anaesthesia than propofol in children undergoing strabismus surgery. Nonetheless, ketamine should be used with caution in patients with globe injuries and increased intraocular pressure (e.g. glaucoma) because the pressure may increase significantly after a single dose of ketamine.

Hannallah[19] concluded that low-dose IM ketamine was an acceptable pre-induction drug, in difficult paediatric patients who were uncooperative during other methods of induction such as inhaled induction of anaesthesia. The rapporteur acknowledges that IV administration may be difficult in children who are uncooperative or with challenging venous access. Consequently, it may be reasonable to offer a single IM injection of ketamine in these situations, as recommended in the guideline 'Sedation in children and young people' by the National Clinical Guideline Centre.[63]

The following studies looked at the combination of ketamine and other agents for anaesthesia:

- **Irving et al**[15] concluded that no additional clinical benefits were observed with fentanyl plus ketamine, compared to ketamine alone.
- **Begec et al**[16] concluded that the administration of ketamine with propofol, preserved hemodynamic stability and reduced the time to the return of spontaneous breathing during ProSeal laryngeal mask airway placement. **Tomatir et al**[20] concluded that IV administration of low dose ketamine prior to propofol induction and infusion can decrease adverse hemodynamic effects commonly encountered when using propofol alone, without changing recovery time and quality in children undergoing MRI. Further studies are warranted to determine the optimum infusion rate of propofol with co-administration of ketamine for preventing movement in different age groups in children.

In the indication of anaesthesia, the above publications were provided. The rapporteur concludes that no significant new information on efficacy or safety has been elucidated and no updates to the product information are thereof warranted from these publications.

ii. Anaesthesia and analgesia

Gharavifard et al[21] conducted a single-blind clinical study to compare 2 routes of administration namely IV and IM for efficacy and rate of complications in 240 children aged between 3 months and 15 years. The study population was distributed into 2 groups of 120 patients each by block randomization method to receive ketamine as IV (1.5 mg/kg) or IM (4 mg/kg). The ketamine efficacy was measured on the basis of pain management and sedation as excellent, moderate and poor. The onset of action of ketamine was 1.7 ± 1.1 minutes and 8.6 ± 3.1 in the IV group and IM group respectively ($p<0.001$). Ketamine exhibited excellent and moderate efficacy in 66.7% and 32.5% in the IV group and 70.0% and 25.0% in the IM group, respectively ($P=0.02$). Optimal sedation was reported for 20.6±12.0 and 37.2±11.8 minutes in the IV and IM groups respectively ($p<0.001$). Compared to the IM group, the tranquil and comfortable recovery was reported by less patients and recovery with brief agitation (requiring rescue dose) was reported by more patients in IV group. (73.3% vs. 90.0%, $p=0.06$ and 26.7% vs. 10.0, respectively). The authors therefore concluded that there was no significant difference between sedative and analgesic effect of IM and IV ketamine. However the onset of action and duration of effect were more desirable in the IV group for suturing, fracture reduction, and foreign body removal.

Rapporteur's comments:
Ketamine is effective when given IV or IM, however there are advantages and disadvantages of both methods. Intravenous administration facilitates the titration of smaller doses of ketamine and therefore reduces the chance of sedation outlasting the intended procedure. A single intramuscular dose is predictable but the intramuscular route of administration can be painful and tends to be reserved for situations when venous access is impractical.
Nonetheless, both routes of administration can be considered and NICE guideline 'Sedation in under 19s: using sedation for diagnostic and therapeutic procedures' recommends ketamine (either intravenous or intramuscular) for children and young people undergoing a painful procedure (for example, suture laceration or orthopaedic manipulation) in whom nitrous oxide and/or midazolam are unsuitable.

iii. Analgesia

Honarmand et al[22] conducted a double-blind, randomised, placebo controlled clinical study to evaluate the efficacy of IV administration of the combination of ketamine and peritonsillar infiltration of tramadol in comparison with single use of each drug for control of postoperative pain in 120 children aged between 2 and 15 years selected for elective adenotonsillectomy. They were randomly divided into 4 groups of 30 each and received IV ketamine 0.5 mg/kg (Group 1), peritonsillar infiltration of tramadol 2 mg/kg (Group 2), IV ketamine 0.5 mg/kg added to peritonsillar tramadol 2 mg/kg (Group 3) and IV and peritonsillar infiltration of 0.9% saline (Group 4). Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) was used to assess postoperative pain level which was recorded every 15 minutes until 1 hour after surgery and later at 2, 4, 6, 8, 16, and 24 hours after surgery. There was a significant difference in the median of sedation scores between the 4 treatment groups at the time of arrival to the post-anaesthesia care unit (PACU) and 15 minutes after that ($p<0.05$). Patients in Group 1 and 3 were comparatively more sedated than the patients in Group 2 and 4 at arrival to PACU ($P<0.05$). The CHEOPS scores were significantly lower in Group 3 compared to others at all times till 24 hours after surgery ($p<0.05$). Further comparison between other groups showed that the CHEOPS score was significantly lower in Group 2 compared to Group 4 till 4 h after surgery ($p<0.05$). Time to the first oral intake was significantly lower ($p<0.05$) and the first time for rescue analgesic requirement was significantly greater ($P<0.001$) in Group 3 compared to other treatment groups. There was no statistical difference among four groups in heart rate, SPO_2 level, blood pressure, vomiting or nausea. But dysphagia was significantly lower in Group 3. The authors therefore concluded that the combined use of IV ketamine 0.5 mg/kg with peritonsillar infiltration of tramadol 2 mg/kg provided better and more prolonged analgesic effects compared with using each drug alone.

Marcus et al[23] performed a double-blind clinical study to compare the effect of IM ketamine with morphine on post-operative analgesia in 80 children aged between 6 and 15 years undergoing elective tonsillectomy, tonsillectomy, and grommet insertion. The children were randomised into 2 groups of 40 each to receive either ketamine 0.5-0.6 mg/kg or morphine 0.1-0.15 mg/kg IM into the anterolateral aspect of the thigh after induction of standard general anaesthetic before surgery. The time taken for the first additional anaesthesia requirement was noted. Pain was assessed by 2 methods, firstly by a 5 point faces scale where 1 is no pain and 5 is highest pain and secondly by CHEOPS. The mean time to awaken was significantly longer in the ketamine group (20.1 minutes vs. 14.2 minutes, $p<0.01$). Both the faces and CHEOPS pain scores were greater in the ketamine group during the first 30 minutes after extubation, however the scores were later similar to morphine group at 1, 2, 3, and 4 hours after extubation. Rescue medicine was required by 1 patient in each group and hence these 2 patients were excluded from the study due to protocol violation. Additional analgesia was provided to similar number of patients in both the groups. There were no differences in the incidence of vomiting or dreaming between the groups. The authors therefore concluded that ketamine may be a useful substitute for morphine in children undergoing tonsillectomy

Safavi et al[24] conducted a randomised, double-blind, placebo-controlled study to investigate the effect of preoperative 0.5 mg/kg IV dexamethasone in combination with 0.5 mg/kg IV ketamine on pain and early oral intake in 120 children aged between 2 and 12 years. The children were randomly allocated to receive either a single dose of dexamethasone 0.5 mg/kg IV as Group D ($n = 30$), ketamine 0.5 mg/kg IV as Group K ($n = 30$), dexamethasone 0.5 mg/kg IV and ketamine 0.5 mg/kg IV as Group KD ($n = 30$) or an equivalent volume of saline as Group C ($n = 30$) at 15 minutes before the induction of anaesthesia. The observational pain score (OPS) was noted to assess the post-operative pain. A low OPS score was reported in Group KD which was significant when compared to all other groups at the time of arrival to the PACU, and at 15, 30, 45, and 60 minutes and also at 1, 2, 4, 6, 12, and 24 hours after operation ($p<0.05$). However, OPS scores were not significantly different between Group K and D. The median sedation values at any postoperative period were not significantly different among the groups. The post-operative analgesic requirement was low in Group KD compared to Group C ($p<0.05$) and Group D or Group

K (p<0.001). The time taken for first oral intake was lower in Group KD compared to other groups (p<0.05). The authors therefore concluded that the use of prophylactic preoperative single dose of IV 0.5 mg/kg dexamethasone in combination with a single dose of IV 0.5 mg/kg ketamine in patients undergoing tonsillectomy reduces postoperative pain and progresses oral intake compared with the individual use of these drugs.

Cha et al[25] conducted a prospective, double-blind, randomised study to investigate the analgesic effects of low-dose ketamine on IV patient-controlled analgesia (IV-PCA) with fentanyl for pain control following the Nuss procedure for pectus excavatum in 60 children aged between 6 and 16 years. The patients were randomly distributed into 2 equal groups to either receive fentanyl (Group F) or fentanyl and ketamine (Group FK). Each group received 0.5 µg/kg/hour of fentanyl or 0.5 µg/kg/hour of fentanyl plus 0.15 mg/kg/hour of ketamine which was infused via an IV-PCA. The intensity of pain was assessed using a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst imaginable pain). A significantly lower VAS pain scores was observed in Group FK than in Group F at 6, 24, and 48 hours after surgery (p<0.05). Additional analgesic, ketorolac was required by 7 patients in Group FK compared to 18 patients in Group F during 48 hours of surgery (23% vs. 53%, P <0.01). The addition of low-dose ketamine to fentanyl showed a considerable decrease in pain scores after Nuss procedure in paediatric patients. The incidence of nausea/vomiting and ondansetron use in Group FK was significantly lower than in Group F (p<0.05). There were no reports of respiratory depression, hallucination or dreaming.

Barois et al[26] conducted an observational pilot study to evaluate the feasibility and efficacy of short venous catheter insertion and immediate ketamine analgesia for tracheal intubation of 57 preterm newborns at birth in the delivery room. Among these newborns, 15 received no analgesia and 39 received IV ketamine (mean dose 1.8 ± 0.9 mg/kg), administered via a short venous catheter. Due to failure of short venous catheter insertion, 3 newborns were excluded from the study. Of these 3 newborns, ketamine was administered by nasal route (mean dose 4.1 ± 0.1 mg/kg) in 2 patients and by rectal route (mean dose 2.2 mg/kg) in 1 patient. The pain threshold during the tracheal intubation procedure was based on a validated acute pain rating scale for term and preterm neonates (APN). In the ketamine group, the mean pain score on the APN scale was 3.6 ± 2.5 before the tracheal intubation procedure (vs. 1.1 ± 1.8 in the no analgesia group, P <0.01) and 0.4 ± 0.7 during the procedure (vs. 2.9 ± 3.2 in the no analgesia group, p<0.001). The heart rate nadir during tracheal intubation was 150.7±29.6 bpm (vs. 112±35.5 bpm in the no analgesia group). No difference in morbidity was observed between the two groups. This pilot study showed that short venous catheter insertion followed by immediate analgesia with ketamine and atropine was effective in lessening pain and preventing vagal bradycardia during tracheal intubation of preterm newborns in the delivery room.

Romanowski et al[27] performed a matched cohort review of 22 patients admitted over a 2 year period to evaluate the efficacy of ketamine infusions in children following tangential excision and skin grafting. Low dose continuous infusion of ketamine (2-3 µg/kg/minute) was administered to 11 patients in addition to standard post-operative pain control for the first 24 hours following their initial excision and grafting (ketamine group), while the other group of 11 patients only received standard post-operative pain control (non-ketamine group). Richmond Agitation-Sedation Scale (RASS) and observational pain scales were used to assess sedation and pain levels. The RASS score was -0.8 ± 0.5 vs.-0.9 ± 0.7 and mean observational pain score was 1.0 ± 0.9 vs. 1.1 ± 0.7 in the ketamine and non-ketamine group respectively. Difference was seen in the individual mean observational pain scores as 8 out of the 11 patients who received ketamine had a mean pain score <1 while only 4 out of 11 in the non-ketamine group had mean pain score <1. There were no adverse effects related to ketamine in this study. The authors therefore concluded that the use of ketamine infusion in post-operative burn may help enhance the activity of pain medications.

O'Flaherty et al[28] conducted a randomised, double-blind, placebo-controlled study to evaluate the effects of ketamine and magnesium in 80 children aged between 3 and 12 years undergoing tonsillectomy. The children were randomly divided into 4 groups of 20 each and received ketamine 0.15 mg/kg (KP group), magnesium sulphate 30 mg/kg (MP group), ketamine 0.15 mg/kg plus magnesium sulphate 30 mg/kg (KM group), or placebo (PP group) IV 5 minutes prior to the initiation of surgery. Pain was assessed using a modified Hannallah pain scale in the PACU. There was no significant difference in the post-operative pain among the groups. At discharge, all patients in all the 4 treatment groups experienced low OPS scores. The initial sedation scores were relatively high as most of the patients were not extubated until their appearance in the PACU. A trend towards decreased sedation was observed in all the 4 groups during their PACU stay and also at discharge. Fentanyl was administered to a higher percentage of patients in the PP group compared to the patients in KP, MP, and KM group in the PACU (70% vs. 50%, 40%, and 53% respectively). However, this difference was not statistically significant. The level of pain reported at home was similar between the groups. Acetaminophen consumption in the first 24 hours was also similar between the groups. More codeine was consumed post-operatively by patients in KP and MP group compared to PP group in the first 24 hours of surgery. The PACU recovery time was similar between the 4 treatment groups (KP group: 70 ± 5 minutes, MP group: 58 ± 6 minutes, KM group: 59 ± 5 minutes, and PP group: 64 ± 5 minutes). There were no differences among the groups in the incidence of nausea, vomiting, sedation, bleeding, or dreaming postoperatively. The authors therefore concluded that no decrease in pain or analgesic consumption was observed in children undergoing tonsillectomy when pre-treated with a small dose of ketamine and/or magnesium.

Haque et al[29] performed a retrospective study to evaluate the efficacy and safety of procedural sedation and analgesia (PSA) by paediatric intensivist for oncology procedures in 124 children aged between 6 months and 14 years The children received 499 procedures (lumber puncture (324), bone marrow biopsy (175), combined lumbar puncture and bone marrow biopsy (40). A small-dose of ketamine (0.5mg/kg) and intermittent doses of propofol (1 mg/kg) was administered IV until required. All procedures were completed successfully indicating success of sedation. All patients tolerated the procedure well without any major adverse events. There were few transient respiratory adverse events which resolved with minor interventions. Low-dose ketamine and propofol were reported to be safe and highly effective in facilitating painful procedures in paediatric population.

Eghbal et al[30] study conducted a double-blind, randomised controlled study to evaluate the effect of IV low dose ketamine (0.25 mg/kg) during induction of anaesthesia on postoperative pain and emergence agitation following adenotonsillectomy in 66 children aged between 5 and 15 years. Patients in the ketamine group (n = 33) received 0.25 mg/kg of ketamine and those in the control group (n = 33) received normal saline. The Wong-Baker FACES Pain scale was used for assessing pain on a scale of 0-10. Results indicated that the pain scores, the percentage of patients requiring paracetamol for postoperative pain control and the EA score was lower in the ketamine group than the control group (P = 0.002). The authors therefore concluded that IV low dose ketamine at induction of anaesthesia may reduce postoperative pain following adenotonsillectomy, paracetamol need as a rescue analgesic, and EA.

Inanoglu et al[31] conducted a double-blind, randomised controlled study to investigate the effects of a multimodal analgesic regimen including IV ketamine and peritonsillar infiltration of bupivacaine, on postoperative pain in 90 children aged between 2 to 12 years undergoing tonsillectomy. Group I (n = 30) received IV and peritonsillar saline, group II (n = 30) received IV saline and peritonsillar bupivacaine, and group III (n = 30) received IV 0.5 mg/kg ketamine and peritonsillar 0.25% bupivacaine (3–5 ml per tonsil). A modified CHEOPS (mCHEOPS) was used to assess the pain intensity over a scale of 0-2 at fixed intervals after the procedure at 15 minute and 1, 4, 12, 16, and 24 hour postoperatively. The mean mCHEOPS score at 15 minutes, 1 hour

and 4 hours was higher in Group I compared to Group II and at all-time intervals than group III ($p<0.05$). Time to first postoperative analgesic request was significantly longer in the ketamine group than in the other groups ($p<0.05$). The authors therefore concluded that IV ketamine and peritonsillar infiltration with bupivacaine were safe and effective as part of a multimodal regime for post-tonsillectomy pain management.

Sareenmaa et al[32] conducted a randomised, double-blind, cross over study to assess the suitability of ketamine for relief of pain caused by tracheal suction during ventilator treatment in 16 newborn infants (10 boys and 6 girls). The children received either IV Ketamine as random infusions of 0.5 mg/kg, 1 mg/kg and 2 mg/kg or placebo. Pain scores were recorded using a behavioural pain score ranging over 0-8. The results indicated that the increase in the pain score caused by the suction from a median baseline level of 0 was significant (P=0.001) after placebo. A similar increase was found after the ketamine doses of 0.5 mg/kg (P=0.001) and 2 mg/kg (P=0.004). It was only after the administration of 1 mg/kg was an attenuation of the pain score change found (P=0.043) compared with placebo. The increase in heart rate and arterial blood pressure in response to tracheal suction were not attenuated by ketamine. The authors therefore concluded that IV ketamine administered during the first few days of life had only a small or moderate analgesic effect on the pain caused by endotracheal suction.

Priestley et al[33] conducted a study to evaluate the efficacy of ketamine in 28 children aged between 1.5 and 12 years of age undergoing painful procedures within the emergency department. Patients received ketamine doses of 1.0 to 1.5 mg/kg IV or 3 to 4 mg/kg IM.
Adjuncts such as atropine (0.02 mg/kg) and midazolam (0.02 mg/kg) were given at the time of ketamine administration. Results indicated that the onset of sedation was quicker in IV route (2.0 min) as compared to the IM route (3.7 min). The time to discharge following ketamine administration averaged 93.9 min (range 67–145 min) in the IV group and 112.3 min (range 78–180 min) in the IM group. Side-effects included vomiting, rash, diplopia, salivation and one case of a distressing emergence reaction. On telephone follow up 1-3 days after the sedation, no delayed adverse events were reported. The authors therefore concluded that ketamine sedation could be effectively and safely used in children requiring immobilization to perform painful procedures.

Betremieux et al[34] conducted a study to assess the effects of a single dose of 5 mg/kg of ketamine administered IV to critically ill preterm infants prior to epicutaneo-caval catheterization by using pulsed wave Doppler ultrasound. Ten (10) critically ill, mechanically ventilated preterm infants, weighing 670-1885 g with gestational ages ranging between 26 and 33 weeks (30.2 ± 2.6) were enrolled in the study at a postnatal age of 1-10 days. A single IV dose of 5 mg/kg of ketamine was injected before central vein catheterization. Systolic, diastolic and mean arterial pressures (SAP, DAP, MAP), HR cardiac output, transcutaneous oxygen pressure (TcPO2), transcutaneous carbon dioxide pressure (TcPCO2), end-diastolic velocity (EDV), peak systolic velocity (PSV), mean arterial velocity (MAV) of the cerebral anterior artery and Pourcelot's resistance index (PRI) were measured before and every minute after ketamine injection (Tk) up to the 10th minute. At minute 2 (T2), a new measurement of cardiac output was registered, and the placement of the catheter began at minute 5 (T5). In all the patients there was a significant ($p<0.05$) fall in SAP, DAP and MAP at T2, which remained significant until T5 while HR, cardiac output, TcPO2, TcPCO2, EDV, PSV, MAV, and PRI did not vary significantly. The authors therefore concluded that ketamine provided major comfort to the baby during painful procedures and considerably facilitated difficult thin vessel catheterisation.

Rapporteur's comments:

Several publications discussed the use of ketamine as analgesic for tonsillectomy procedures:

- **Honarmand et al**[22] concluded that the combined use of IV ketamine 0.5 mg/kg with peritonsillar infiltration of tramadol 2 mg/kg provided better and more prolonged analgesic effects compared with using each drug alone.
- **Marcus et al**[23] concluded that ketamine may be a useful substitute for morphine in children undergoing tonsillectomy.
- **Safavi et al**[24] concluded that the use of prophylactic preoperative single dose of IV 0.5 mg/kg dexamethasone in combination with a single dose of IV 0.5 mg/kg ketamine in patients undergoing tonsillectomy reduces postoperative pain and progresses oral intake compared with the individual use of these drugs.
- **O'Flaherty et al**[28] concluded that no decrease in pain or analgesic consumption was observed in children undergoing tonsillectomy when pre-treated with a small dose of ketamine and/or magnesium.
- **Eghbal et al**[30] concluded that IV low dose ketamine at induction of anaesthesia may reduce postoperative pain following adenotonsillectomy, paracetamol need as a rescue analgesic, and EA.
- **Inanoglu et al**[31] concluded that IV ketamine and peritonsillar infiltration with bupivacaine were safe and effective as part of a multimodal regime for post-tonsillectomy pain management.

Ketamine is approved for diagnostic and operative procedures of ear, nose, and mouth and appears to be an effective analgesic agent for these procedures.

The following publications reported on the efficacy of ketamine as analgesia after painful procedures:

- **Cha et al**[25] concluded that the addition of low-dose ketamine to fentanyl showed a considerable decrease in pain scores after Nuss procedure in paediatric patients. The incidence of nausea/vomiting and ondansetron use in Group FK was significantly lower than in Group F ($p<0.05$). There were no reports of respiratory depression, hallucination or dreaming.
- **Romanowski et al**[27] concluded that the use of ketamine infusion in post-operative burn may help enhance the activity of pain medications.
- **Haque et al**[29] reported that low-dose ketamine and propofol were reported to be safe and highly effective in facilitating painful procedures in paediatric population.
- **Priestley et al**[33] concluded that ketamine sedation could be effectively and safely used in children requiring immobilization to perform painful procedures.

In the indication 'analgesia', the Guidelines on the management of postoperative pain[69] report that IV ketamine has been evaluated as part of multimodal analgesia. In adults and children, studies found IV ketamine infusions were associated with decreased postoperative pain medication use compared with placebo, and in some studies with decreased postoperative pain scores. IV ketamine was also associated with decreased risk of persistent postsurgical pain. In the trials, ketamine was administered preoperatively, intraoperatively, and/or postoperatively, at widely varying doses. There was insufficient evidence to determine the optimal method for dosing ketamine, but the panel suggests using a preoperative bolus of 0.5 mg/kg followed by an infusion at 10 mg/kg/min intraoperatively, with or without a postoperative infusion at a lower dosage. Clinicians who administer ketamine should be familiar with its use and adverse effects, and the panel suggests that ketamine be reserved for major surgeries. Some situations in which ketamine might be particularly useful include management of highly opioid-tolerant patients and patients who have difficulty tolerating opioids.

Use of ketamine in babies and preterm newborns

- **Barois et al**[26] showed that short venous catheter insertion followed by immediate analgesia with ketamine and atropine was effective in lessening pain and preventing vagal bradycardia during tracheal intubation of preterm newborns in the delivery room.
- **Betremieux et al**[34] concluded that as ketamine provided major comfort to the baby during painful procedures and considerably facilitated difficult thin vessel catheterisation.
- **Sareenmaa et al**[32] therefore concluded that IV ketamine administered during the first few days of life had a small or moderate analgesic effect on the pain caused by endotracheal suction.

The above articles support the use of ketamine in newborns and preterm infants when clinically appropriate and no particular safety concern has been elucidated.

iv. Analgesia and sedation

Pees et al[35] studied the effects of racemic ketamine and (S)-ketamine in 100 paediatric patients (ages 2 days-11 years) undergoing cardiac catheterization.11 He found that, when administering either IV doses of 1 mg/kg racemic ketamine or 1 mg/kg (S)-ketamine, the combination of (S)-ketamine and midazolam was more efficient with regards to dosage of sedative agents and side effects in newborns and children when compared with racemic ketamine. The dosage of (S)-ketamine was significantly lower than that of racemic ketamine (2.28 mg/kg/h versus 3.12 mg/kg/h, p=0.037). While moderate side effects were reported for both (S)-ketamine and its racemate, severe side effects were reported to occur more often in children treated with the racemic solution. An analysis of the analgesic/sedative dosages by age groups (neonatal/infant group 0-1 year: 2.68 mg/kg/h, toddlers 1-3 years: 2.74 mg/kg/h, and older children 3-11 years: 2.55 mg/kg/h) showed no significant difference.

Auletta et al[36] assessed the efficacy and safety of atropine-midazolam-ketamine regimen as a sedative and analgesia in oncology patients undergoing painful procedures. Overall, 69 patients of mean age 7.3 ± 4.4 years underwent 255 procedures using an infusion of atropine (0.01 mg/kg) and midazolam (0.05 mg/kg) over 5 minutes, followed by an infusion of ketamine (up to 2.0 mg/kg) over an additional 5 minutes. The clinical efficacy rate was observed to be 91%. No additional medication was required for further sedation or analgesia in 232 procedures while 23 procedures (9.0%) required additional midazolam and/or ketamine. The 3 most frequent transient effects were hypertension in 71 procedures (27.8%), hypotension in 53 procedures (20.8%), and tachycardia in 49 procedures (19.2%). Twenty-five procedures (9.8%) had associated complications. Ten procedures (3.9%) had ketamine associated emergent reactions, ranging from laughing and verbosity to screaming and crying. Nine procedures (3.5%) were associated with nausea, vomiting, or dry heaving, and 2 (0.8%) were associated with shaking chills after procedure completion. The clinically significant adverse event (defined as baseline deviation requiring acute medical intervention to prevent or ameliorate clinical deterioration) rate was 1.6% (n = 4, all during lumbar punctures). In 1 case, the procedure was terminated prematurely because of laryngospasm; in 3 cases oxygen supplementation was required because of hypoxemia. Clinically significant adverse events were associated with younger patients and increased ketamine doses. None of the adverse events had long-term sequelae. The authors therefore concluded that the atropine-midazolam-ketamine regimen was noted to be efficacious as an analgesic and sedative and demonstrates an acceptable safety profile in the larger proportion of the patients who underwent painful oncology procedures.

Mason et al[37] established a protocol in 2 phases for administering ketamine to induce sedation and analgesia during interventional radiological procedure. The aim of the first phase was to develop a sedation protocol to replace general anaesthesia for specified paediatric interventional procedures. Patients (n = 6) with difficulty in IV access received a single dose of IM ketamine (3-

6 mg/kg). For sedation shorter than 10 minutes, patients received IV ketamine (0.5-1.0 mg/kg) and for more than 10 minutes of sedation, patients received IV bolus ketamine (1-2 mg/kg) immediately followed by IV infusion of ketamine (25-150 µg/kg/minute). In phase 2, the results of phase 1 were reviewed and a formal ketamine protocol was developed. Overall 38 patients with a mean age of 9.9 ± 8.5 years were included in the phase I study. There were no failures nor substantial adverse events occurred with respect to sedation in phase 1. All sedations occurred for a mean duration of 52 ± 28 minutes (10-120 minutes). The sedation time was longer in the patients who received ketamine through infusion than in those who received ketamine as bolus (46 ± 20 minutes vs 28 ± 22 minutes, P = 0.02). There were no reports of prolonged sedation in any patient. The authors therefore concluded that ketamine-induced sedation was found to be an effective alternative to general anaesthesia for interventional radiologic procedures in paediatric patients.

Erden et al[38] conducted a prospective, randomised study to compare 2 methods of IV anaesthesia namely ketamine and propofol/fentanyl anaesthesia in 40 children aged between 3 months and 15 years of age during extracorporeal shockwave lithotripsy (ESWL). All patients received intranasal midazolam 0.3 mg/kg premedication. Patients were randomly assigned to propofol/fentanyl (PF; n = 20) group on odd days and ketamine (K; n = 20) group on even days. Group K received a bolus of IV atropine 0.01 mg/kg and IV ketamine 2 mg/kg before the start of the procedure and group PF received IV propofol 3 mg/kg and IV fentanyl 1 µg/kg with induction and an infusion of propofol 1 mg/kg/hr continued throughout the procedure. Both groups were evaluated for recovery time (RT), discharge time (DT), and procedural time (PT). Procedural time and DT were similar in the 2 groups whereas the recovery time was significantly longer in Group K compared to Group PF ($p<0.05$). Compared with Group PF, intra-procedural complication incidence was lower with Group K. Post-procedure adverse reactions with Group K include nausea, vomiting, hallucinations and agitation, with no need for medication. The author concluded that midazolam premedication with ketamine and propofol/fentanyl provided efficacious sedation and analgesia during ESWL in children.

Miyamoto et al[39] conducted a prospective, randomised, double-blind study to evaluate the efficacy of intraoperative ketamine in controlling the post-operative agitation in 105 cleft palate infants aged between 10 and 23 months undergoing soft palate plasty (n=72) or hard palate plasty (n=33). Patients were randomly assigned to receive either sevoflurane (S) or isoflurane (I) for maintenance of anaesthesia and ketamine (K) or 5% glucose (C: control) for adjunctive anaesthetic. Blinded solution(BS) containing either K (2 mg/ml) or C was administered IV (induction with 0.5 ml/kg before incision, maintenance with 0.5 ml/kg/hr to the end of the surgery).Based on the anaesthetics and surgery, patients were classified into 8 groups: control-sevoflurane-soft palate plasty (C-S-SP, n=21), ketamine-S-SP (K-S-SP, n = 21), C-S-hard palate plasty (C-S-HP, n = 9), K-S-HP (n = 9), C-isoflurane-SP(C-I-SP, n = 15), K-I-SP (n = 15), C-I-HP (n = 7) and K-I-HP (n = 8). Results indicated that the ketamine group showed lesser agitation in comparison with control group ($p<0.05$). However, it was reported that patients belonging to the K-S-SP and K-I-SP groups exhibited more agitation than those of K-S-HP and K-I-HP, respectively, despite the same combinations of anaesthetics ($p<0.05$). The authors therefore concluded that the pain and discomfort due to airway narrowing in post palatoplasty was successfully reduced by intraoperative ketamine.

Lauretti et al[41] conducted a study evaluating the impact of IV ketamine on analgesia and to analyse the outcome in children. A total of 24 children were given an initial dose of sevoflurane/02, followed by 10 ug/kg IV atropine. The patients in the control group (CG), dipyrone group (DG), ketamine group (KG) and ketamine/dipyrone Group (K/DG) were randomised to receive IV saline, 10 mg/kg dipyrone, 0.2 mg/kg ketamine and 10 mg/kg dipyrone + 0.2 mg/kg ketamine respectively. Parameters recorded in this study were pain score, sedation score and nausea score on VAS at 24 hours on a 10 cm scale. Time to first request for analgesia and number of analgesic doses

used in first 24 hours were recorded. Results showed that ketamine groups like KG- 525 ± 341 and KDG-1170 ± 373 presented greater time to start the rescue analgesics when compared to CG- 3.7 ± 0.5 and DG- 2.2±1. Also, the study suggested that CG=DG<KG ($p<0.002$) < KDG, which was statistically significant. Pain scores at 24 hours evidenced by VAS evaluation were significantly lesser in K/DG, compared to the CG ($p<0.05$). Nausea 20 minutes after tracheal extubation and 24-hour nausea/vomiting impression were similar among groups.

Svenson et al[40] conducted a retrospective study to review the experience in the use of ketamine in a regional air ambulance service and suggested indications for its use in the prehospital setting. All patients were transported by a regional aeromedical program. Ketamine was used in 40 patients of age range between 2 months and 75 years. Of the 40 patients, 23 were trauma patients, 4 had burns, 4 were cardiac patients, and 9 were for other medical issues, mostly respiratory. Most of the patients received only 1 dose of ketamine, but 12 patients needed repeated doses to maintain analgesia during flight. Doses of ketamine ranged from 1 mg/kg IV to 5 mg/kg IM, if IV access had not been established. Intramuscular (IM) doses were used for pain control and relief of agitation before extrication in 1 patient because of combativeness and inability to establish IV access in another 3. In all burn patients, ketamine was used for pain control and sedation and had reported with significant pain relief. In the cardiac patients, ketamine was used for sedation as they were hypotensive and intubated. In the asthma patients, ketamine was used for sedation. In trauma patients, most received ketamine for sedation and analgesia. In 8 patients, ketamine was used for pain control. In 3 of them, ketamine was used for pain control before extrication with or without IV access, the others had significant pelvic or long bone injuries and had no relief of pain with narcotics. In 5 patients, ketamine was used as an aid to procedural sedation. In the cardiac and trauma patients, none had reported blood pressure drop following ketamine administration. The authors concluded that ketamine is an ideal drug for use in many prehospital situations. They also suggested ketamine is effective and safe and may be more appropriate than drugs currently used by prehospital providers.

The results of a retrospective database review were reported by **Bredmose et al**.[70] Ketamine was administered to 164 children (3 months- 15 years) in a paediatric trauma setting. The results suggest that a mean dose of 1.0 mg/kg IV did not result in any major side effects and no complications were associated with the use of ketamine in these paediatric patients.

A medical responder reported on the administration of ketamine to trauma patients in prehospital care. **Porter**[71] examined the use of ketamine 2 mg/kg IV in 32 patients (9-87 years) requiring analgesia/anaesthesia prior to arrival at the hospital. He concluded that ketamine was safe and effective with general anaesthesia occurring within 30-60 seconds and persisting for 10-15 minutes. Repeated bolus doses of 1-3 mg/min maintained this effect.

Rapporteur's comments:
Pees et al[35] found that, when administering either IV doses of 1 mg/kg racemic ketamine or 1 mg/kg (S)-ketamine, the combination of (S)-ketamine and midazolam was more efficient with regards to dosage of sedative agents and side effects in newborns and children when compared with racemic ketamine. An analysis of the analgesic/sedative dosages by age groups (neonatal/infant group 0-1 year: 2.68 mg/kg/h, toddlers 1-3 years: 2.74 mg/kg/h, and older children 3-11 years: 2.55 mg/kg/h) showed no significant difference.

Auletta et al[36] concluded that the atropine-midazolam-ketamine regimen was noted to be efficacious as an analgesic and sedative and demonstrates an acceptable safety profile in the larger proportion of the patients who underwent painful oncology procedures.

Mason et al[37] concluded that ketamine-induced sedation was found to be an effective alternative to general anaesthesia for interventional radiologic procedures in paediatric patients.

Erden et al[38] concluded that midazolam premedication with ketamine and propofol/fentanyl provided efficacious sedation and analgesia during extracorporeal shockwave lithotripsy in children.

Miyamoto et al[39] concluded that the pain and discomfort due to airway narrowing in post palatoplasty was successfully reduced by intraoperative ketamine.

Lauretti et al[41] reported that the group of patients in which ketamine is used presented greater time to start the rescue analgesics when compared to control group and dipyrone group. Pain scores at 24 hours evidenced by VAS evaluation were significantly lesser in ketamine/dipyrone group, compared to the control group ($p<0.05$).

Svenson et al[40] concluded that ketamine is an ideal drug for use in many prehospital situations such as trauma, burns, and in cardiac patients. They also suggested ketamine as effective and safe and may be an appropriate choice by prehospital providers. Similarly, **Porter**[71] examined the use of ketamine 2 mg/kg IV in 32 patients (9-87 years) requiring analgesia/anaesthesia prior to arrival at the hospital. He concluded that ketamine was safe and effective with general anaesthesia occurring within 30-60 seconds and persisting for 10-15 minutes. Repeated bolus doses of 1-3 mg/min maintained this effect. **Bredmose et al.**[70] suggest that a mean dose of 1.0 mg/kg IV did not result in any major side effects and no complications were associated with the use of ketamine in paediatric patients in a trauma setting.

The above publications support the use of ketamine for its sedative and analgesic effects in children. No safety concerns are apparent from these articles.

v. Sedation

Cotsen et al[42] evaluated the use of racemic ketamine as sedation in 211 children for interventional radiologic procedures. When doses of either 2 mg/kg IV or 3 mg/kg IM were administered to children ages 3 days to 10 years, excellent sedation and analgesia was noted. One subject, a 7-week old male infant who was born prematurely, experienced apnoea which resolved completely after assisted ventilation for several breaths. The report concluded that the short induction time, rapid recovery, and minimal respiratory depression are features that make this sedative appropriate for interventional radiology.

The review by **Dolansky et al** suggests that ketamine is safe and effective for sedation in children.[43] The ability to treat patients without the need to routinely support ventilation, the known sympathomimetic events (increases in blood pressure and heart rate), and the wide range of safe dosing of ketamine make it an attractive option. Commonly used doses for IM administration were 2-4 mg/kg and in 'recent studies' 4-5 mg/kg IM and 0.5-2.0 mg/kg IV.
Dolansky also notes that much higher doses were used in the 1970s (7 mg/kg to 15 mg/kg IM) without an increase in reports of adverse events.

Various paediatric sedation methods were reviewed by **Green et al** in a two-part series in 1990.[44] A ketamine dose of 4 mg/kg IM was administered to 108 children (ages 14 months to 13 years) requiring sedation for minor procedures in the emergency department. In most cases (86%), a single ketamine dose was effective for analgesia, sedation and immobilisation. During the data collection period, one case of emesis followed by laryngospasm was reported in a patient

with a history of asthma and “easy gagging”. This event resolved without intubation or noted sequelae. The author notes that, after the data collection period for this paper, a second case of emesis-associated laryngospasm occurred.
This patient was reported to have a history of asthma and “easy gagging” as well but a correlation between these factors in a patient’s history and laryngospasm is unclear. Though the incidence rates of these events remain low, as a precaution, the author recommends that paediatric ketamine sedation be performed under the supervision of physicians trained in intubation. This article also recommends that ketamine sedation be reserved for patients greater than 12 months of age because of concerns about airway complications in younger children. The authors conclude that ketamine is efficacious, allows a shorter recovery time and has a safety profile consistent with similar sedatives.

In the second part of this series, **Green et al**[45] summarizes the available literature related to the administration of ketamine in paediatric patients. In total, 97 reports with over 17,000 ketamine administrations were reviewed. Nearly 11,600 of those cases were specifically reported as use in paediatric patients. The authors note that respiratory function after dosing with ketamine in children remains intact and that most treated patients were routinely monitored only by medical staff observation. Doses reported in this publication range from 0.25 - 11 mg/kg IV and 0.5 - 17 mg/kg IM with dissociation effects seen at doses of 1 – 2 mg/kg IV and a minimum of 4 mg/kg IM. The article concludes that, because of a wide safety margin and predictable onset of activity and recovery time, ketamine should be more widely used in the emergency department setting, especially in paediatric patients.

A review of IM administration of ketamine by emergency physicians to paediatric patients was reported by **Green et al (1998)**.[46] Doses of 4 mg/kg were administered to 1008 children ranging in age from 4 months to 15 years. Patients less than 3 months were excluded from this protocol because of concerns about airway complications in these patients. Seven of the 1008 patients, ranging in age from 17 months to 10 years, experienced respiratory-related adverse events; 4 patients experienced transient laryngospasm, 2 patients experienced apnoea and 1 patient experienced respiratory depression. None of these patients required intubation, all procedures were completed, and recovery was “uneventful”. This study concluded that ketamine is highly effective, has a wide margin of safety, allows for alternative administration routes and preserves the protective airway response.

The **Clinical Practice Guidelines for Emergency Department Ketamine Dissociative Sedation** originally prepared by Green as reported above were updated in 2011.[1] While a number of areas in this guideline were updated (route of administration [IV preferred over IM] and co-administered medications [prophylactic anticholinergics no longer recommended and routine prophylactic benzodiazepines no longer recommended for children]), most pertinent is the update to previously reported contraindications. In previous guidelines, ketamine was not recommended for patients between 3 and 12 months of age because of concerns about airway complications. The 2011 update removes the restriction for patients between 3 and 12 months of age. However, age less than 3 months remains as a contraindication in this protocol as the author notes that these patients are more susceptible to airway complications. The author also notes that differences in infant-specific anatomy may be more responsible for these complications than ketamine itself. In this protocol, a racemic ketamine loading dose of 1.5-2.0 mg/kg IV was recommended for children. A racemic ketamine dose of 4-5 mg/kg was recommended for IM administration in children, if IV access could not be secured. The author concludes that available literature supporting the use of ketamine in children is “robust” with few issues left unstudied.

A prospective audit of ketamine use in paediatric procedures was reported by **Ellis et al**.[47]
The IM administration of 4 mg/kg to 89 children (ages 1-10 years) requiring procedural sedation was reviewed. No serious adverse events were reported. Survey forms were presented to all

parents/care givers. All of those who responded selected “very satisfied/satisfied” with their overall experience. A high percentage (94%) of parents reported that, if the need presented, they would have ketamine administered to their children again. The authors conclude that ketamine is safe and effective when administered in the emergency department.

Tarek Tammam[48] conducted a double-blind study to compare the efficacy of IM ketamine, dexmedetomidine, and a mixture of both for paediatric magnetic resonance imaging (MRI) sedation in 162 children aged between 2 and 7 years. The children with American Society of Anesthesiologists (ASA) physical status I-II, planned for elective MRI were equally distributed into 3 groups, namely Group D who received IM dexmedetomidine 3 µg/kg, Group K who received IM ketamine 4 mg/kg, and Group DK who received a combination of IM dexmedetomidine 1.5 µg/kg and ketamine 2 mg/kg. The onset of satisfactory sedation was significantly shorter in the DK group in comparison with the D group (4.8 ± 1.6 minutes vs. 16.8 ± 4.5 minutes, $p<0.05$), while no significant difference was observed between the DK and K group (4.6 ± 1.5 minutes). The duration of sedation was significantly higher in K group compared to D and DK group (47.8±4.5 minutes vs. 25.8± 3.6 minutes and 24.7 ± 3.1 minutes respectively, P = 0.030). Also the discharge time was significantly greater in the K group compared to DK group and D group (54.9 ± 3.7 minutes vs. 29.9±2.1 minutes and 37.2 ± 5.3 minutes respectively, P = 0.030). A remarkably lower rate of sedation failure was reported in the DK group compared to Group K and Group D (5.6% vs. 22.2% and 27.8% respectively, P = 0.007). Also the use of rescue midazolam was significantly lower in the DK group compared to the K and D groups (0.03 ± 0.12 mg vs. 0.21 ± 0.41 mg and 0.24 ± 0.41 mg respectively, P = 0.002). None of the patients experienced episodes of hypotension or bradycardia in the DK and K groups while four patients (7.4%) experienced episodes of hypotension and five patients (9.3%) experienced episodes of bradycardia in the D group.
The authors therefore concluded that with respect to the onset of action, sedation failure rate and hemodynamic stability, the combination of IM dexmedetomidine and ketamine was found to be superior to the individual drugs in paediatric MRI sedation.

Edge and Morgan[49] conducted a study to evaluate the efficacy of ketamine sedation in 16 patients (9 males and 7 females) aged between 13 months and 7 years undergoing radiotherapy. Patients were injected an initial dose of ketamine 5 mg/kg IM titrated to a maximum induction dose of 12 mg/kg. Results indicated that the patients achieved adequate sedation. Supplementary ketamine was required only in 20 instances (7%) only. Respiratory obstruction due to excessive salivation occurred in 3 patients at supine position before radiotherapy. Vomiting was common particularly in those with leukaemia on cytotoxic drugs.
Hallucination was noted in one patient. No laryngospasm or pulmonary complications were noted. The authors therefore concluded that ketamine was beneficial in providing satisfactory sedation in children undergoing radiotherapy treatment.

Green et al[50] conducted a prospective, study to evaluate the efficacy and safety of procedural sedation with IM ketamine (4 mg/kg IM) in 108 children aged between 14 months and 13 years. Results indicated that fully adequate sedation, analgesia, and immobilization were produced by a single ketamine dose alone in 93 cases. One 18-month-old child vomited shortly after injection and experienced transient laryngospasm with cyanosis; intubation was not required, and there were no adverse sequelae. Airway patency and independent respirations were fully maintained in all other patients; no hemodynamic instability occurred at any time. There were no other clinically significant complications. Emesis well into the recovery phase was noted in 6% of the patients. Nightmares were not observed. Overall parental reaction to the use of ketamine sedation was strongly positive. The authors therefore concluded that ketamine could be used effectively by emergency physicians to facilitate procedural sedation in children aged 12 months to 15 years.

Mason et al[51] conducted a prospective study to evaluate the results of a pilot program for nursing sedation using IV ketamine infusions in 39 children aged between 1 and 18 years.

The patients received IV ketamine, 1-2 mg/kg as bolus followed by an IV infusion of ketamine, 25-125 µg/kg/minute during the interventional radiological procedures. Prior to ketamine administration, patients were given IV glycopyrrolate 0.005 mg/kg. In addition, children greater than 5 years received IV midazolam, 0.1 mg/kg and not exceeding 3 mg. The dosages of ketamine, and the sedation and recovery durations were recorded. Results indicated procedural success in patients without sedation failures. Average duration of all sedations was 53 minutes. The mean ketamine sedation dosage was found to be 1.5 mg/kg. On an average recovery was established within 30 minutes. The authors therefore concluded that ketamine was effective in providing paediatric sedation.

Barr et al[52] conducted a prospective study to determine the sedative effects of IV ketamine and fentanyl combined with nitrous oxide/oxygen on blood pressure, pulse, respiration, oxygen saturation, and behaviour, and to report intra- and post-treatment complications on paediatric dental patients in a private practice setting. A total of 27 patients of mean age of 34 months were studied. Patients were treated with IV ketamine and fentanyl at dosages of 0.5 mg/kg and 0.5 µg/kg, respectively for every 15-20 minutes of interval period. Results showed that the pulse rate was elevated from a normal value of 104 to 125, an increase of 20%. The mean blood pressure across all subjects during treatment was elevated 12% from the baseline (112/64). The respiration rate averaged 23 breaths per minute. Mean behaviour composite scores were 1.9 at the initial examination and 3.3 during treatment. Based on these findings the authors concluded that IV sedation of pre-cooperative healthy paediatric patients with ketamine, fentanyl, and nitrous oxide/oxygen appeared to be a safe and effective sedation modality by providing the practitioner an alternative to general anaesthesia.

Pruitt et al[53] conducted a study on 37 children aged between 12 months and 7 years scheduled for oral-maxillofacial procedure, involved IM infusion of 3 mg/kg ketamine, 0.05 mg/kg midazolam, and 0.005 mg/kg glycopyrrolate. Around 70% patients had excellent sedation and the remaining 30% patients showed acceptable sedation. However, 5 patients required IM infusion of 1 mg/kg ketamine to complete the procedure. It was noticed that the time to recovery ranged from 50-120 minutes. On average, there was an 18% increase in pulse rate and 13% increase of respiratory rate. No dysrhythmias, airway obstruction or laryngospasm were noted.

In a study by **Petrack, Marx, and Wright**[54], patients aged between 6 months and 6 years were administered IM ketamine 4 mg/kg and atropine 0.01 mg/kg. All patients experienced acceptable sedation. The time to recovery and discharge ranged from 75-96 minutes. Increase of heart rate and blood pressure were noted. No patients required airway support or supplemental oxygen.

In a recent study by **Van Wijhe, Stricker, and Rejger**[55], IV ketamine was given to 68 patients aged 4 months -17 years. An acceptable sedation was achieved by using a starting dose of IV midazolam from 0.05 mg/kg-0.1 mg/kg. Patients were given a maximum single dose of 2 mg and a maximum total dose of 4 mg of midazolam. Midazolam sedation was followed by IV ketamine 1.0-2.0 mg/kg. Additional 0.5-1.0 mg IV ketamine intervention was required in few patients, to a maximum total dose of 6 mg/kg. Postoperative recovery time ranged from 15-120 minutes. On an average 70% patients recovered within 30 minutes. No serious complications were encountered; no patient required intubation, bag or mask ventilation. Cardiac parameters were relatively stable with increase of blood pressure and heart rate. 1% patients experienced drop in oxygen saturation below 85% that required interruption of the procedure and hypoxia correction.

Seigler et al[56] conducted a retrospective study to compare ketamine and propofol sedation in children aged between 1 month and 22 years undergoing diagnostic and therapeutic procedures. In all, 405 procedures were performed (261 procedures with propofol and 144 with ketamine). The mean time from administration of the first dose of medication until the patient woke up was 36.6 (15.0) minutes for the propofol group and 69.2 (43.2) minutes for the ketamine group. The mean

time to awakening was significantly longer for the ketamine group, even after adjusting for the length of the procedure (P = 0.0001). Patients were significantly more likely to have airway (p =0.01) or hemodynamic (p =0.002) effects with propofol than with ketamine. One patient in the propofol group and two in the ketamine group received endotracheal intubation due to airway effects. The authors concluded that both propofol and ketamine provided safe and effective sedation for the short, painful procedures performed.

Bleiberg et al[57] conducted a retrospective study to evaluate whether lower doses of ketamine in the range of 0.5 to 1.0 mg/kg could successfully sedate 72 paediatric patients aged between 10 months and 14 years undergoing procedural sedation. Patients received an initial minimum dose of 0.02 mg/kg and 0.05 mg/kg and not exceeding the maximum dose of 1 mg and 4 mg of IV atropine and IV midazolam respectively. Patients were then administered a total IV ketamine dose ranging from 0.5 mg/kg to a maximum of 2 mg/kg. The results showed that 88% (95% CI, 0.78-0.94) of paediatric patients in the emergency department (ED) achieved adequate sedation with IV ketamine doses ranging from 0.5-1.0 mg/kg. It was also found that younger patients required higher dose of ketamine than older children (r = -0.227; P = 0.055). Thirty-nine (39) patients achieved parental satisfaction, 38 were highly satisfied or satisfied and 1 patient was dissatisfied with the procedural sedation because of inadequate pain control. The authors therefore concluded that there was a potential role for low-dose IV ketamine in the range of 0.5 to 1.0 mg/kg for paediatric procedural sedation. Most paediatric ED patients could be successfully sedated with 1 mg/kg of ketamine.

Gayatri et al[58] conducted a prospective, randomised, open-label study assessing the safety and efficacy of 2 different doses of ketamine in propofol-ketamine combination (PKC), administered IV in children undergoing cardiac catheterisation procedures (CCP). Thirty-two (32) children aged < 5 years with American Society of Anaesthesiologists grade II to III, undergoing either interventional or diagnostic CCP were randomised to receive continuous IV administration of ketamine at 25 µg/kg per minute (Group 1; n=15) or ketamine at 12.5 µg/kg per minute (Group 2; n=17) with a fixed dose of propofol (25 µg/kg per minute) in PKC. Mean blood pressure, HR, arterial oxygen saturation, respiratory rate, airway status (occurrence of any “critical airway incident”), episodes of unpredictable spontaneous movement that occurred with the procedure were noted. There was no hemodynamic instability, airway compromise, excessive salivation, or arterial desaturation in either of the groups. Although statistically insignificant, the occurrence of unpredictable spontaneous movements that interfered during CCP, were less frequent among group 1 patients as compared to group 2. Patients received additional doses of ketamine only to control spontaneous movements (11 children in group 1 and 13 in group 2). The total dose of ketamine used in group 1 and group 2 were 309.25 ± 90.97 µg/min and 148.06 ± 34.05 µg/min, respectively. Further, the time taken to regain consciousness was greater in group 1 as compared to group 2 (60 ± 54.87 minutes vs 20.13 ± 17.08). The authors therefore concluded that the combination of propofol (25 µg/kg per minute) with either doses of ketamine (25 and 12.5 µg/kg per minute, respectively) was safe and efficacious for CCP in children.

Heilbrunn et al[59] conducted a retrospective chart review of paediatric patients undergoing procedural sedations so as to determine which among the 2 commonly used ketamine intravenous dosing regimens (1 mg/kg [k1.0] vs 1.5 mg/kg [k1.5]) required more administered doses and also assessed if differences existed between k1.0 and k1.5 in the total dosage, total mg/kg, and time to recovery. Cohorts were compared on the basis of the number of doses, mg/kg administered, total dosage (mg), and adverse events. In all, 346 patients were included, with 159 patients in k1.0 and 187 patients in k1.5. The primary outcome measure was the number of doses of ketamine required to complete the procedural sedations in the k1.0 and k1.5 groups. The secondary outcome measures included the total dosage administered, total mg/kg administered, and time to completion of the procedure. The number of patients requiring 2 or fewer doses compared with those receiving triple dosing was also determined. Patients in the k1.5 group required fewer

median doses of ketamine as compared to the k1.0 group (1.0 vs. 2.0, P = 0.02). Patients in the k1.0 group had a higher median overall mg/kg dosage than those in the k1.5 group (1.71 mg/kg vs. 1.60 mg/kg; p<0.01). This indicated that adopting a k1.5 protocol decreased the median number of doses from 2 to 1. In addition, k1.5 decreased the median mg/kg administered compared with k1.0. Also, k1.5 showed a decrease the number of sedations requiring a third dose of ketamine to complete sedation as compared with k1.0 (7.57 vs. 18.47%, P = 0.002). The k1.0 and k1.5 groups showed no statistically significant difference in the median time to completion. The authors therefore concluded that most ketamine sedations could be completed with a single dose when patients are initially dosed at 1.5 mg/kg and recommended that practitioners consider standard dose of 1.5 mg/ kg/dose for procedural sedations using ketamine.

Meyer et al[60] in a prospective study assessed the inter- and intra-individual variability in ketamine dosage for sedation in repetitive invasive procedures in 25 children of median age
12 years with malignancies. A total of 92 procedures (58 lumbar punctures, 34 bone marrow biopsies) were evaluated. Sedation consisted of midazolam (0.1 mg/kg slowly IV, 1 min prior to ketamine) and ketamine (0.5–1.0 mg/kg slowly IV). Incremental doses of ketamine were given (0.33 mg/kg) to patients if necessary to achieve or maintain deep sedation. Primary outcome measure assessed was the inter- and intra-individual ketamine dosage required to achieve adequate sedation. Secondary outcome measures assessed were the number of procedures with adequate sedation (Ramsay score of >4) and the need for therapeutic interventions. A great variability in both inter- and intra-individual ketamine dosage required to achieve deep sedation (Ramsay score > 4) was seen. However, inter-individual variability in ketamine dosage was substantially higher than intra-individual variability. Inter- and intra-individual variability in ketamine dosage was not affected by the type of procedure (lumbar puncture vs. bone marrow aspiration). In 88 procedures (95.7%) sedation was considered satisfactory (Ramsay scale 6: 60 procedures, 65.3%; Ramsay scale 5: 28 procedures, 30.4%). In 4 procedures (4.3%), sedation was considered unsatisfactory (Ramsay scale: 4). In these procedures, ketamine dosage was higher than in successfully completed sedation procedures (0.30 mg/kg/min). Patients who experienced a drop in oxygen saturation (5.4% of procedures) recovered spontaneously, or by changing postural position and/or by applying oxygen via a mask. The authors conclude that due to great inter- and intra-individual differences, ketamine dosage should be titrated toward the desired level of sedation. Thus, ketamine can be adjusted to the individual's need while achieving adequate sedation.

Green et al[61] conducted a retrospective analysis of the database of a prospective case series to quantify the dose–response of ketamine with respect to sedation adequacy and time to discharge in order to identify an optimal dose in patients from 1,022 consecutive children aged ≤15 years. The children were administered ketamine IM in the emergency department of a university medical centre. The adequacy of sedation and time to discharge were compared with dose administered. Initial ketamine doses averaged 3.96 ± 0.69 mg/kg, with a range 0.48 to 9.09 mg/kg. Children judged to be adequately sedated received higher doses than those with inadequate sedation (3.94 ± 0.44 mg/kg vs 3.77 ± 0.49 mg/kg, P = 0.041) and a non-significant trend was noted toward uniformly adequate sedation with increasing dose (≤91% at <4.00 mg/kg, 93% at 4.00–4.49 mg/kg, and 100% at ≥4.50 mg/kg). The authors therefore concluded that ketamine doses of 4 to 5 mg/kg IM produced adequate sedation in 93–100% of children, suggesting that this dosing range may be optimal for emergency department procedural sedation. No difference in time to discharge was observed for lower or higher doses.

Rapporteur's comments:

- The following publications discuss the doses of ketamine used for *sedation or anaesthesia*:

Cotsen et al[42] reported excellent sedation and analgesia when doses of either 2 mg/kg IV or 3 mg/kg IM were administered to children ages 3 days to 10 years.
Dolansky et al[43] concluded that commonly used doses for IM administration were 2-4 mg/kg and in 'recent studies' 4-5 mg/kg IM and 0.5-2.0 mg/kg IV. The authors also noted that much higher doses were used in the 1970s (7 mg/kg to 15 mg/kg IM) without an increase in reports of adverse events.
Petrack, Marx, and Wright[54] reported that patients aged between 6 months and 6 years were administered IM ketamine 4 mg/kg and atropine 0.01 mg/kg.
In a study by **Van Wijhe, Stricker, and Rejger**[55], IV ketamine was given to 68 patients aged 4 months -17 years. Midazolam sedation was followed by IV ketamine 1.0-2.0 mg/kg. Additional 0.5-1.0 mg IV ketamine intervention was required in few patients, to a maximum total dose of 6 mg/kg.
Heilbrunn et al[59] concluded that most ketamine sedations could be completed with a single intravenous dose when patients are initially dosed at 1.5 mg/kg and recommended that practitioners consider standard dose of 1.5 mg/kg/dose for procedural sedations using ketamine.
Meyer et al[60] concluded that due to great inter- and intra-individual differences, ketamine dosage should be titrated toward the desired level of sedation. Thus, ketamine can be adjusted to the individual's need while achieving adequate sedation.
Green et al[61] concluded that ketamine doses of 4 to 5 mg/kg IM produced adequate sedation in 93–100% of children, suggesting that this dosing range may be optimal for emergency department procedural sedation. No difference in time to discharge was observed for lower or higher doses.
Gayatri et al[58] concluded that the combination of propofol (25 µg/kg per minute) with either doses of ketamine (25 and 12.5 µg/kg per minute, respectively) was safe and efficacious for cardiac catheterisation procedures in children.

In the above publications, the doses used were in the range 0.5-2 mg/kg IV and 2-5 mg/kg IM. It is also noted that when the ketamine is used in conjunction with other anaesthetic agents e.g. propofol, there is a reduction in the dose of ketamine. The reported doses appear in line with the current SmPC dosage recommendations of ketamine in children. No particular safety concern was reported.

- *In the emergency department (ED),* ketamine is reported to be a popular agent to facilitate painful procedures in children. The following publications provide perspectives of using ketamine in the ED:

In their first series (1990), **Green et a**l[44] recommended that ketamine sedation be reserved for patients greater than 12 months of age because of concerns about airway complications in younger children. The authors also concluded that ketamine is efficacious, allows a shorter recovery time and has a safety profile consistent with similar sedatives.
In the second part of this series, **Green et al**[45] concluded that, because of a wide safety margin and predictable onset of activity and recovery time, ketamine should be more widely used in the emergency department setting, especially in paediatric patients. Further, in a later publication, **Green et al**[46] concluded that ketamine is highly effective, has a wide margin of safety, allows for alternative administration routes and preserves the protective airway response.
The Clinical Practice Guidelines for Emergency Department Ketamine Dissociative Sedation originally prepared by Green as reported above were updated in 2011.[1] The 2011 update removes the restriction for patients between 3 and 12 months of age. However, age less than 3 months remains as a contraindication in this protocol as the author notes that these patients are more susceptible to airway complications. The author concluded that available literature supporting the use of ketamine in children is "robust" with few issues left unstudied.
Ellis et al[47] concluded that ketamine is safe and effective when administered in the emergency department (ages 1-10 years).

Bleiberg et al[57] reported that there was a potential role for low-dose IV ketamine in the range of 0.5 to 1.0 mg/kg for paediatric procedural sedation based on their observations in paediatric patients aged between 10 months and 14 years .

The rapporteur notes that there is a clinical practice guideline regarding the administration of ketamine for ED procedural sedation and analgesia (The Clinical Practice Guidelines for Emergency Department Ketamine Dissociative Sedation, updated in 2011). It is acknowledged that this guideline aims to provide the best available evidence and perspectives of ketamine sedation practice.
Although the clinical guideline states that 'age less than 3 months' is a contraindication in the ED protocol, the authors advised that the propensity towards airway adverse events is not particular to ketamine but rather represents infant-specific differences in airway anatomy and reactivity and laryngeal excitability. It is noteworthy that the authors concluded that the ED ketamine literature in children is robust and there is already a strong evidentiary basis in place for indications, dosing, route, and adjunctive medications and for the safety of this drug in the ED.
The rapporteur acknowledges that clinical practice guidelines are in place in the ED to facilitate the effective and safe use of ketamine in children. There may be contraindications based on age but it is recognised that this is based on infant physiology and possibly the clinical expertise available in the ED under emergency circumstances rather than ketamine itself. It is also reassuring that the guidelines state that available literature supporting the use of ketamine in children is 'robust'.

In the radiology setting:
Tarek Tammam[48] concluded that with respect to the onset of action, sedation failure rate and hemodynamic stability, the combination of IM dexmedetomidine and ketamine was found to be superior to the individual drugs in paediatric MRI sedation.
Edge and Morgan[49] concluded that ketamine was beneficial in providing satisfactory sedation in children undergoing radiotherapy treatment.

General use of ketamine as sedative:
Mason et al[51] concluded that ketamine was effective in providing paediatric sedation.
Barr et al[52] concluded that IV sedation of pre-cooperative healthy paediatric patients with ketamine, fentanyl, and nitrous oxide/oxygen appeared to be a safe and effective sedation modality by providing the practitioner an alternative to general anaesthesia.
Pruitt et al[53] reported that around 70% patients had excellent sedation and the remaining 30% patients showed acceptable sedation.
Seigler et al[56] conducted a retrospective study to compare ketamine and propofol sedation in children aged between 1 month and 22 years undergoing diagnostic and therapeutic procedures. The authors concluded that both propofol and ketamine provided safe and effective sedation for the short, painful procedures performed.

Overall, the benefit:risk balance of using ketamine for its sedative properties remains unchanged. Evidence from published literature indicates that it can be used for children of all ages with appropriate medical supervision as advised in the SmPC.

V. MAH SAFETY DATA

The MAH assessed the safety of ketamine in the clinical development program and continuously monitored the post-marketing safety profile since commercialization in 1969.
Periodic Safety Update Reports (PSURs) have been routinely provided for ketamine. Throughout the period spanned by the submitted PSURs (1 May 2008 to 8 December 2012), the risk-benefit

profile of ketamine has remained favourable, and review of cases involving paediatric patients did not identify any new paediatric safety information.

A cumulative search of the MAH's post-marketing safety database was conducted up to 31 July 2015 to identify adverse event reports following the use of ketamine in the paediatric population (patients < 18 years old). In total, 194 paediatric reports were identified, representing 13.3% (n = 1462) of all ketamine adverse event reports in the MAH's post-marketing safety database.

Table 2 represents the most frequently reported (> 5%) PTs following the use of ketamine in paediatric patients.

Preferred Term	Number of Cases	% (n = 194)
Drug ineffective	22	11.3
Accidental overdose	15	7.7
Oxygen saturation decreased	14	7.2
Sedation	13	6.7
Vomiting	12	6.2
Seizure	10	5.2
Bradycardia	10	5.2

Neurotoxicity

Green et al[64] presented the clinical perspectives of ketamine and neurotoxicity and noted no adverse neurologic sequelae observed from 42 Emergency Department series totalling almost 10,000 children.

Additionally, a number of studies conducted in infants aiming to examine neurofunctional effects of ketamine have been published.

- **Bhutta et al**[65] conducted a pilot randomized, double-blind, placebo- controlled trial evaluating 24 infants who were treated randomly with either ketamine or placebo (saline) prior to cardiopulmonary bypass surgery. The authors found no significant changes from pre-anesthetic values in either S-100b levels or Bayley Scales of Infant Development–Second Edition scores, although slightly better (but insignificant) neurodevelopmental scores were observed in the ketamine treatment group.
- In another prospective follow-up cohort study conducted by **Guerra et al**[66], 95 infants ≤ 6 weeks of age underwent open heart surgery (53 received ketamine) were measured for neurodevelopmental outcomes at 18 to 24 months of age. No evidence of an association between adverse neurodevelopmental outcomes and the dose or duration of the administered sedation or analgesia drugs has been identified.
- **Yan et al**[67] conducted a prospective study in 49 children less than 2 years old scheduled for outpatient laser surgery treatment of benign facial growths. It was observed that repeated exposure (3 times) of ketamine was associated with a decrease of mental and psychomotor development index 3 days post-surgery as measured by Bayley Scales of Infant Development-Second Edition (mental development index (pre vs post values): 95.2+ 10.0 versus 90.2+ 10.3; psychomotor development index (pre vs post values):88.8 + 6.3 versus 83.6 + 6.9), whereas no such effect was observed after 1 or 2 exposures. Due to the limitations inherent in the design (the very short follow-up 3 days post-surgery and the uncontrolled design), it cannot be determined whether the observations reflect a transient condition post-surgery/anaesthesia or a clinically meaningful long-term effect on neurodevelopment. Neither can it be determined whether ketamine itself or the surgical stress/pain and postsurgical inflammatory response are more associated with the observed results. The observed decrease in mental/psychomotor development index is also of doubtful clinical significance.

Inadvertent overdosing

Green et al[68] conducted a study to characterize the clinical manifestations, outcome, and aetiology of inadvertent ketamine overdose in the emergency department (ED). The cases of inadvertent ketamine overdose in children seen in the ED were solicited through electronic mail subscription lists or reported to the Institute for Safe Medication Practices. Results indicated that 9 cases of inadvertent ketamine overdose were seen in children treated in the ED. Overdoses were either 5 (n = 3), 10 (n = 5), or 100 (n = 1) times the intended dose administered either by the IM (n = 5) or IV (n = 4) route. All 9 experienced prolonged sedation (3 to 24 hours). The authors therefore concluded that overdoses in healthy children are associated with prolonged sedation.

MAH conclusion on safety profile of ketamine in children

The MAH concludes that currently, there is no definitive evidence of ketamine-specific persistent brain injury or cognitive loss resulting from its clinical application in paediatric population. Based on the review of the published studies described above and the review of the post-marketing database, the MAH considers that the safety profile of ketamine observed in paediatric patients is similar to that in the adult population and consistent with the product labelling.

Rapporteur's comments:

Out of the most frequently reported PTs presented in Table 2, seizures are not listed in section 4.8 of the SmPC and warrant further evaluation. Tonic clonic movements are listed as undesirable effect of ketamine but reference to seizures or convulsions is not made in the SmPC. The MAH is requested to provide a summary of the 10 paediatric cases of seizures and discuss any causal association with ketamine (see section VIII).

VI. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

The rapporteur concludes that based on the data provided as part of this European paediatric work-sharing procedure under Article 45, the benefit/risk balance of ketamine remains unchanged for the paediatric population.

However, the MAH is requested to provide additional information, as detailed in Section VIII Request for supplementary information.

VII. COMMENTS FROM MSS AT DAY 85

Following the circulation of the Day 70 PPdAR, the rapporteur received the following comments from one member state:

The Preliminary Assessment Report refers only to the UK SmPC, however for a complete assessment, the various national SmPCs of Ketamine (which are not identical to the UK SmPC) should also be taken into consideration prior to come to the conclusion "unchanged benefit risk". The MAH should be asked to submit those.

A statement about the age groups in which Ketamine is indicated should be added to section 4.1 of the SmPC.

Rapporteur's comments:

In light of the above comments received, the MAH is requested to propose a statement about the paediatric age groups in which ketamine is indicated in section 4.1 of the SmPC.

It is acknowledged that the various national SmPCs of ketamine may not be identical to the UK SmPC. A review of the various national SmPCs in the national language will not be possible within the scope of this paediatric work-sharing procedure. However, the MAH should submit the core SmPC in English version that is used in various member states and the paediatric statements in the SmPCs of various member states in a tabulated form.

VIII. REQUEST FOR SUPPLEMENTARY INFORMATION

- The MAH is requested to provide a summary of the 10 paediatric cases of seizures and discuss any possible causal association with ketamine.
- The MAH is requested to propose a statement about the paediatric age groups in which ketamine is indicated in section 4.1 of the SmPC.
- The MAH is requested to submit the core SmPC in English version that is used in various member states and the paediatric statements in the SmPCs of various member states in a tabulated form.

IX. MAH RESPONSES TO THE PRELIMINARY PDAR DAY 90

i. Question 1:

The MAH is requested to provide a summary of the 10 paediatric cases of seizures and discuss any possible causal association with ketamine.

MAH response:

The MAH performed a search in their post-marketing safety database.

- **Methodology**

The MAH's safety database contains cases of AEs reported spontaneously to the MAH, cases reported by the health authorities, cases published in the medical literature, cases from MAH-sponsored marketing programmes, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality. The original safety database search was conducted for paediatric cases where ketamine was reported as a suspect medication through 31 July 2015. In order to make the results described in this response more current, the search was updated for cases that involved paediatric patients (defined as cases where the patient's age was reported to be ≤17 years, or the patient was described as a neonate, infant, child, or adolescent) and included an AE that encoded to the MedDRA (v. 19.1) PT Seizure reported through 31 January 2017.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete and follow-up information may not be available.
An accumulation of AE reports does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

- **Results**

In addition to the 10 cases identified by the original search included in the Article 45 response, this updated search identified 1 additional case, for a total of 11 paediatric cases that involved the PT Seizure. Selected characteristics of these 11 cases are presented in Table .

Table 3. Selected Characteristics of Ketamine Paediatric Cases That Involved the MedDRA (Version 19.1) Preferred Term Seizure Reported Through 31 January 2017

Selected Characteristic		No. of Cases
Age: Range = 4 months to 13 years Median = 6 years n = 9	≤27 Days	-
	28 Days to 23 months	2
	2 to 11 years	8
	12 to 17 years	1
Gender	Female	2
	Male	7
	Unknown/not reported	2
Case seriousness	Serious	7
	Non-serious	4
Case outcome	Recovered	8
	Not recovered	2
	Unknown / not reported	1
Report source	Literature	3
	Spontaneous	8
Country where event occurred	Japan	6
	United Kingdom	2
	France	1
	Germany	1
	United States	1
Medically confirmed	Yes	10
	No	1

MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

When the patient's age and gender were reported, most were children aged 2-11 years and most involved male patients. Most of the cases were assessed as serious because of the seizure event. The seizure event was reported to have resolved in the 8 cases where the patient recovered and had not resolved in the 2 cases where the patient had not recovered. All but 1 case was medically confirmed.
The indications for ketamine use in 8 of the 11 cases were for use as anaesthesia or analgesic therapy that is consistent with the listed indications for ketamine, while in 3 cases, ketamine was used for peri-procedural sedation. In none of the cases was the seizure reported to be associated with ketamine abuse. The dose of ketamine was reported in 8 cases, and appears to be consistent with the recommended doses of ketamine described in the MAH's ketamine Core Data Sheet (CDS).

Latency to seizure onset in these cases ranged from immediately after ketamine administration to 12-24 hours after start of a ketamine infusion, to 15 hours after ketamine administration. In 1 case, the seizure onset was after the patient received 3 divided doses over 50 minutes for a total of 55 mg.
Two (2) cases were poorly described, and contain insufficient information for evaluation.
In 1 case, there appears to be an alternate cause for the seizure. This case involved a 3-year-old girl with a history of Rett syndrome who had received anaesthesia with ketamine and alimemazine and experienced 6 episodes of seizure-like activity post operatively. Rett syndrome is a severe neurodevelopmental disorder that affects primarily females; seizures occur in more than 60% of Rett syndrome patients, and age at seizure onset is 2-3 years in about 33% of cases.
In most of the remaining cases, the patients appear to have been at increased risk for seizures independently of ketamine exposure. In 7 cases, the patients were reported to have been treated with other medications that have been reported to be associated with seizures, such as amitriptyline, atropine, carbamazepine, cefotaxime, fentanyl, lidocaine, methohexital, metronidazole, morphine, or sufentanil.

Fever is an important risk factor for seizures in children. Although none of the patients in these cases were specifically reported to be febrile at the time of seizure onset, in 2 cases, the patients were reported to have been treated with anti-infectives (cefotaxime and metronidazole; and an unspecified antibiotic, respectively) and had underlying illnesses (rhabdosarcoma and emergency colostomy; and viral bronchitis, respectively) potentially associated with fevers, and the possibility that the patients were febrile at the time of seizure onset cannot be entirely excluded.
Other risk factors that have been reported to be associated with the occurrence of seizures in children include hypoxia, high blood pressure, and congenital vascular malformations. In 2 cases, the patients reported concurrent AEs that encoded to the PTs Respiratory depression, Blood pressure increased, Bradycardia, Hypotension, and Cardiac index decreased, suggestive of increased risk for seizure. It should also be noted that the patient had received ketamine (along with sufentanil, midazolam and milrinone) peri-surgically for cardiac surgery with extracorporeal circulation to correct Fallot's tetralogy. This case was also reported to involve an unspecified drug interaction.

These 11 cases are summarised in Table 4.

Table 4. Ketamine Cases of Adverse Events That Encoded to the MedDRA (Version 19.1) PT Seizure in Paediatric Patients Reported Through 31 January 2017

Age/Gender/ Weight/Source	Total Daily Dose/Route	Adverse Events (as MedDRA PTs)	Indication	Suspect Medications	Concomitant Medications	Medical History	Action Taken/Case Outcome	Review Comments
3 years/Female/ 13 kg/ Literature	65 mg/Oral	Application site anaesthesia; Seizure; Eye disorder, Tremor	Anaesthesia prior to 'squint surgery'	Alimemazine; ketamine	Halothane; Nitrous oxide; Oxygen	Rett syndrome	Not applicable/ Recovered	Ketamine administered was 1 hour prior to surgery. Surgery was uneventful. Recovery was slow, and patient experienced 6 episodes of seizure-like activity. The patient slept for 8 hours and experienced 2 more seizures. Patient has Rett syndrome, and seizures are a frequent complication with onset often at about age 3 years.
10 years/Male/ 32.7 kg/ Spontaneous	5 mg/mL/ Intravenous	Seizure	Tumour pain	Ketamine	Amitriptyline; Carbamazepine; Cefotaxime; Filgrastim; Metronidazole; Morphine; Ondansetron; Topotecan	Recurrent sacro-coccyygeal rhabdosarcoma; emergency colostomy	Permanently withdrawn / Recovered	Seizure onset 12-24 hours after starting ketamine infusion. Ketamine infusion was discontinued and the patient was treated with phenytoin.
4 months/ Male/Unspecified/ Spontaneous	20 mg/kg/hour/ Unspecified	Seizure; Hepatic enzyme increased	Artificial ventilation sedation	Ketamine	Unspecified antibiotics; Dobutamine; Epinephrine; Ipratropium; Methohexital; Midazolam	Respiratory syncytial virus bronchitis; premature delivery with bronchopulmonary dysplasia	Unknown/Not recovered	The reporting physician stated that he believed that the events were not related to ketamine.

Table 4. Ketamine Cases of Adverse Events That Encoded to the MedDRA (Version 19.1) PT Seizure in Paediatric Patients Reported Through 31 January 2017

Age/Gender/ Weight/Source	Total Daily Dose/Route	Adverse Events (as MedDRA PTs)	Indication	Suspect Medications	Concomitant Medications	Medical History	Action Taken/Case Outcome	Review Comments
Child of unspecified age / Unspecified / Unspecified / Literature	Unspecified/ Intravenous	Seizure	Sedative therapy	Ketamine	Unspecified	Unspecified	None/ Recovered	Case not well described. Seizure described as not serious.
7 years/ Male/Unspecified/ Spontaneous	200 mg/ Intramuscular	Seizure; Respiratory depression; Blood pressure increased; Heart rate increased	Anaesthesia prior to entropion correction for both eyes	Ketamine	Atropine	Unspecified	Not Applicable/ Recovered	Onset of seizure immediately after ketamine administration. Events gradually resolved.
6 years/ Male/ 25.2 kg / Spontaneous	55 mg/ Intravenous	Seizure	Sedation prior to magnetic resonance imaging	Ketamine; Triclofos	Atropine	Autism/Lipoma	Permanently withdrawn/ Recovered	Ketamine dose administered as 25 mg, 15 mg and 15 mg over course of about 50 minutes. Seizure onset after 3rd dose of ketamine.
5 years/ Male/Unspecified/ Spontaneous	20 mg / Intravenous	Seizure	Pain and Sedation prior to bone marrow aspiration	Ketamine	Unspecified	Congenital aplastic anaemia	Post-therapy/ Recovered	Seizure onset at some unspecified time on the same day after ketamine administration. The reporting paediatrician considered the seizure as not serious.

Table 4. Ketamine Cases of Adverse Events That Encoded to the MedDRA (Version 19.1) PT Seizure in Paediatric Patients Reported Through 31 January 2017

Age/Gender/ Weight/Source	Total Daily Dose/Route	Adverse Events (as MedDRA PTs)	Indication	Suspect Medications	Concomitant Medications	Medical History	Action Taken/Case Outcome	Review Comments
13 years/Female/ 43 kg/Spontaneous	90 mg/ Unspecified	Gaze palsy, Muscle tightness, Seizure	Procedural pain post-surgery to correct idiopathic scoliosis	Droperidol; Fentanyl; Ketamine	Unspecified	Scoliosis	Permanently withdrawn / Recovered	Seizure onset about 15 hours after administration of ketamine, fentanyl, and droperidol. All medications were discontinued and the patient recovered.
8 years/ Male/25 kg/ Spontaneous	Unknown (administered '40 mL' of unspecified concentration) / Intravenous	Seizure	Anaesthesia prior to thoracic soft tissue tumour	Ketamine	Atropine; Lidocaine	Mediastinum neoplasm	Permanently withdrawn / Recovered	Seizure onset following ketamine administration and just after starting the procedure. Patient treated with intravenous midazolam. Unknown if the patient had a history of seizures.

Table 4. Ketamine Cases of Adverse Events That Encoded to the MedDRA (Version 19.1) PT Seizure in Paediatric Patients Reported Through 31 January 2017

Age/Gender/ Weight/Source	Total Daily Dose/Route	Adverse Events (as MedDRA PTs)	Indication	Suspect Medications	Concomitant Medications	Medical History	Action Taken/Case Outcome	Review Comments
1.8 years / Male / 10 kg / Spontaneous	15 mg/ Intravenous	Drug interaction, Bradycardia, Hypotension, Cardiac index decreased, Seizure	Post procedural drainage	Ketamine; Sufentanil	Midazolam; Milrinone	Fallot's tetralogy	Permanently withdrawn / Not Recovered	Onset of the AEs at the end of the injection. The patient was treated with ketamine and sufentanil for pain following removal of Redon's drain following cardiac surgery with extracorporeal circulation for Fallot's tetralogy. Treated with cardiac massage and intubation; also received atropine and epinephrine. Reported that there was 'complete haemodynamic recovery within half an hour', however, it was reported that the patient had not recovered at the time the case was reported.
Child of unspecified age / Unspecified / Unspecified / Literature	Unspecified / Unspecified	Seizure	Analgesic therapy	Ketamine	Unspecified	Unspecified	Unknown / Unknown	Case not well described. Seizure described as serious.

AE = adverse event; AER = adverse event reporting; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

In summary, review of the MAH's safety database identified 11 cases that involved AEs that encoded to the PT Seizure in paediatric patients reported through 31 January 2017. None of these cases involved ketamine abuse, and most involved indications consistent with listed indications for ketamine. When the ketamine dosage was reported, most appear to have been consistent with the recommended doses of ketamine described in the MAH's CDS. Most of the patients were reported to have recovered. While 2 of the 11 cases were poorly described, 1 case involved an alternate possible aetiology for the seizure event, and most of the remaining cases appear to have been at increased risk for the seizure event independently of ketamine exposure. In addition, it should be noted that tonic clonic movements, which is listed in Section 4.8 Undesirable effects of the ketamine SmPC and CDS, may resemble clinical manifestation of seizures and be reported as such.
This review of seizure cases that involved paediatric patients reported to the MAH's safety database did not identify any important new safety information that changes the benefit-risk assessment of the use of ketamine in paediatric patients.

Rapporteur's comments:
The MAH provided a comprehensive description of 11 paediatric seizure cases, as retrieved from their post-marketing safety database.
The rapporteur agrees that the review of paediatric seizure cases did not provide evidence of causality with ketamine and did not demonstrate any new safety signal. Issue resolved.

ii. Question 2:

The MAH is requested to propose a statement about the paediatric age groups in which ketamine is indicated in section 4.1 of the SmPC.

MAH response:
With regard to the above request, the MAH conducted a current review of the literature and available clinical information. Upon assessment of the available information, the dosing of ketamine in paediatric patients should be by body weight, as it is in adults.
The dosing should also be in accordance with the general principles outlined earlier in 4.2: *As with all general anaesthetics, the individual response to ketamine varies according to a number of factors including dose, route of injection and body weight of the patient so dosage recommendations cannot be absolutely fixed. The dose should be titrated against the patient's requirements.*
The assessment of the data also concluded that a lower age limit for the use of ketamine in the pediatric population is not supported.

- **Review of Literature**

Methodology
A comprehensive literature search for ketamine and esketamine was performed in MEDLINE, EMBASE, and BIOSIS (dated: 24 March 2017 in all 3 databases) to identify scientific literature articles, systemic reviews, meta-analysis, and guidelines discussing the use and benefits of ketamine in paediatric populations. In addition, guidelines and cited literature from Cochrane systemic reviews were screened to identify supporting information not available in the aforementioned literature databases. The keywords included Ketamine, Esketamine, S-Ketamin, S (+)-ketamine, Ketanest, Ketolar, Ketalar, LI900013, PF01386611, pediatric anesthesia, infant, toddler, juvenile, boy, girl, adolescence, 'minor (person)', puberty, child, preschool child, school child, pediatric surgery, pediatrics, pharmacokinetics, pharmacodynamics, drug dose, drug overdose, drug toxicity.

Results
Approximately 4744 articles were retrieved from the literature search of which 98 articles were considered relevant and are discussed below:

Ketamine Use in Paediatrics

Ketamine is effective in the management of short-term, painful, or emotionally disturbing procedures, laceration repairs, and orthopaedic procedures in the paediatric population. At doses of 1 to 2 mg/kg intravenous (IV) or 4 to 5 mg/kg intramuscular (IM), ketamine is generally effective at producing the dissociative state, with additional incremental doses of 0.5 to 1 mg/kg IV as needed for continued sedation.[72]

In 2009, the French Agency for Safety of Health Products (AFSSAPS) of good practice for the implementation of care and painful procedures in children in France stated that: in low-doses, IV ketamine (0.5 mg/kg not exceeding 2 mg/kg) appears to be the only medication effective for providing sedation and analgesia during painful procedures. The IM route (<4 mg/kg) may be considered an alternative route of administration if the IV route is not readily available; however, the recovery time (RT) of IM ketamine is delayed compared with IV.[73] The major AEs associated with ketamine administration include vomiting, airway obstruction, hypoxia, apnoea, and laryngospasm.[72]

Mechanism of Action

Ketamine is unique among the agents used for procedural sedation and analgesia (PSA) in that it produces a 'dissociative state'. Ketamine causes dissociation between the thalamoneocortical and limbic systems, resulting in a clinical dissociation from the environment. It increases the heart rate and blood pressure by its activation of the sympathetic nervous system. This 'dissociative state' is characterised by potent analgesia, sedation and amnesia whereas cardiovascular stability is maintained and spontaneous breathing and protective airway reflexes are preserved. Due to these properties, ketamine is administered before induction of anaesthesia, to improve haemodynamic stability. It is a drug extensively used in the emergency department for a variety of brief painful or emotionally disturbing procedures such as repair of injuries, reduction of fractures, foreign-body removal, genitourinary procedures, eye procedures, etc. Several studies have shown successful use of ketamine in well-structured sedation programmes with trained personnel.[74, 75, 76]

1. **Pharmacokinetics**

Ketamine is a highly lipid-soluble drug that is associated with large steady-state volume of distribution and rapid clearance. Ketamine is eliminated by hepatic metabolism through N-demethylation to nor-ketamine via cytochrome P (CYP) 3A4, CYP 2B6, and CYP 2C9 enzyme systems.[77] Despite the common use of ketamine in children with cardiac disease, pharmacokinetic (PK) data in this population are sparse. Results from available literature have shown that the degree of ketamine sedation is related to its plasma concentration and that the PK of ketamine in small children is similar to those in adults. Ketamine plasma concentrations following administration of the same constant rate infusion per kg change with body weight (or age).

The following table summarises relevant PK information from studies conducted with ketamine in paediatric patients:

Author	Dose (mg/kg)	Route	Age range	No. of subjects	Conclusions
Allen et al[78]	3 mg/kg	IV	0 to 12 years	21	Sedation should not be delivered according to a pre-set dosage regime (administering a certain dose at defined time intervals) because of great inter- and intra-individual differences in the need for ketamine dosage.

					The dose of ketamine could be adjusted depending on individual needs of the patient while achieving adequate sedation.
Hartvig et al[79]	1 or 2 mg/kg/hour	IV infusion	1 week to 30 months	10	The degree of sedation was related to the plasma concentration of ketamine and that the PK of ketamine in small children was similar to those in adults.
Elkomy et al[77]	2 mg/kg over 5 minutes	IV infusion	6 months to 18 years	21 children with pre-existing congenital heart disease	Ketamine plasma concentrations following administration of the same constant rate infusion per kg change with body weight. The authors concluded that ketamine clearance in children with pre-existing congenital heart disease was comparable to values reported in healthy subjects.
Herd et al[80]	1 to 1.5 mg/kg	IV	8.3 months and 3.5 years	54	Ketamine 1 mg/kg IV provided satisfactory serum concentrations for children undergoing sedation for painful procedures of duration <5 minutes and produces concentrations associated with analgesic effect for >10 minutes.
Grant et al[81]	2 mg/kg IV (n=4) 6 mg/kg IM (n=5)	IV IM	4 to 9 years	9	Smaller plasma ketamine concentrations at 5 hours after IV administration to children and the shorter mean residence time suggested faster elimination. The absorption of ketamine from the IM injection also appeared to be fast.
Herd et al[82]	1 to 1.5 mg/kg	IV	Mean age 8.15 years	43	A concentration of 1 mg/L was associated with a sedation level of 3 or less in 95% of children, while 1.5 mg/L was associated with a sedation level of 2 or less in 95% of children. These concentrations were attained for 3 to 4 minutes after ketamine IV bolus 1 and 1.5 mg/kg, respectively.

Rapporteur's comments:
The MAH also presented three additional studies but the age and number of children included in the studies were not specified. Due to the lack of information on the characteristics of the paediatric population, these studies have not been included in the summary table.
Although limited, the available PK studies in the paediatric population suggest that the degree of sedation is related to the plasma concentration of ketamine. Nonetheless, due to inter- and intra-individual differences, the dosage regimen cannot be pre-set and absolutely fixed. The dosage of ketamine is on a mg/kg basis and should be titrated depending on the individual patient's

requirement. These dosage recommendations are already highlighted in the product information of ketamine.

2. Optimal Dosing

One of the specific qualities of ketamine is that sedation does not deepen despite additional doses once the patient has reached the dissociative sedation state.[86] In a 2011 guideline update, the authors Green et al[1] recommended that the minimum dose at which the dissociative state can be reliably achieved in children is 1.5 mg/kg IV, and the common loading doses are 1.5 to 2.0 mg/kg. Repeated incremental doses of 0.5 to 1.0 mg/kg may be administered if initial sedation is inadequate or if repeated doses are necessary to accomplish a longer procedure. Based on clinical evidence with the IM route, the minimum dose in children at which the dissociative state can be reliably achieved is 4 to 5 mg/kg. Should this initial dose result in insufficient procedural conditions, a repeated half dose or full dose is usually effective. Further, ketamine does not appear to exhibit dose-related AEs within the range of clinically administered doses under standard administration techniques. In a large meta-analysis, the authors Green et al[1] found no dose-related AEs across the standard dosing range, with only unusually high IV doses (i.e. initial dose 2.5 mg/kg or total dose 5.0 mg/kg) increasing the risk of vomiting and slightly increasing the risk of apnoea and recovery agitation. Thus, a higher dose may be considered where appropriate.

The following table summarises relevant information regarding IV or IM dosing of ketamine in paediatric populations:

Author	Dose (mg/kg)	Route	Age range	No. of subjects	Conclusions
Tomatir et al[20]	a 2.5 mg/kg bolus of propofol in 30 seconds followed by an infusion of 100 µg/kg/minute (n = 20), or a bolus 1.5 mg/kg of propofol in 30 seconds immediately after a 0.5 mg/kg rapid bolus of ketamine followed by an infusion of 75 µg/kg/minute (n = 23)	IV	9 days to 7 years	43	IV administration of low dose ketamine prior to propofol induction and infusion can decrease adverse haemodynamic effects commonly encountered when using propofol alone, without changing recovery time and quality in children undergoing MRI. Further studies are warranted to determine the optimum infusion rate of propofol with co-administration of ketamine for preventing movement in different age groups in children.
Bleiberg et al[57]	0.5 to 1.0 mg/kg	IV	10 months to 14 years	72	There was a potential role for low-dose IV ketamine in the range of 0.5 to 1.0 mg/kg for paediatric procedural sedation. Most paediatric emergency department patients could be successfully sedated with 1 mg/kg of ketamine.
Miqdady et al[88]	midazolam (0.05-0.20 mg/kg) followed by	IV	1 to 18 years	301	Ketamine midazolam sedation was effective for diagnostic paediatric gastrointestinal endoscopy.

	ketamine (0.5-2.0 mg/kg)				
Gayatri et al[58]	ketamine at 25 µg/kg per minute (Group 1; n = 15) or ketamine at 12.5 µg/kg per minute (Group 2; n = 17) with a fixed dose of propofol (25 µg/kg per minute) in propofol-ketamine combination.	IV	<5 years	32	The combination of propofol (25 µg/kg per minute) with either doses of ketamine (25 and 12.5 µg/kg per minute, respectively) was safe and efficacious for cardiac catheterisation procedures in children.
Ibacache et al[87]	a single IV dose of 1 µg/kg dexmedetomidine administered over 10 minutes. After that they were randomised to 1 of the 5 groups: Group 1 (ketamine 1 mg/kg), Group 2 (ketamine 1.25 mg/kg), Group 3 (ketamine 1.5 mg/kg), Group 4 (ketamine 1.75 mg/kg), and Group 5 (ketamine 2 mg/kg)	IV	1 to 8 years	25	The addition of 2 mg/kg of ketamine to 1 µg/kg of dexmedetomidine was an effective anaesthetic option to perform a caudal block and then the ensuing superficial lower abdominal or genital surgery of short duration in healthy children.
Betremieux et al[34]	single dose of 5 mg/kg of ketamine prior to epicutaneo-caval catheterisation	IV	Critically ill, mechanically ventilated preterm infants, weighing 670 to 1885 g with gestational ages ranging between 26 and 33 weeks were enrolled in the study at a postnatal age of 1 to 10 days	10	Ketamine provided major comfort to the baby during painful procedures and considerably facilitated difficult thin vessel catheterisation, it may be used in such conditions.

Green et al[61]	Initial ketamine doses averaged 3.96 ± 0.69 mg/kg, with a range 0.48 to 9.09 mg/kg	IM	≤15 years	1022	Ketamine doses of 4 to 5 mg/kg IM produced adequate sedation in 93% to 100% of children, suggesting that this dosing range may be optimal for emergency department procedural sedation. No difference in time to discharge or adverse effects was observed for lower or higher doses.
Meyer et al[60]	midazolam (0.1 mg/kg slowly IV, 1 minute prior to ketamine) and ketamine (0.5-1.0 mg/kg slowly IV	IV	Median age 12 years	25	Due to great inter and intra-individual differences, ketamine dosage should be titrated toward the desired level of sedation. Thus, ketamine can be adjusted to the individual's need while achieving adequate sedation.

Rapporteur's comments:
The MAH presented 3 additional literature articles but due to lack of information on the characteristics of the paediatric population, these 3 studies have not been included.
The dosing regimen used in the studies appears consistent with the dosing recommendation in the product information. Ketamine can also be administered as supplement to anaesthetic agents (e.g. propofol) and in this clinical situation, the dose of ketamine may be reduced accordingly.
No new information regarding the dosing of ketamine in children has been identified from the studies.

3. Clinical Efficacy and Safety

The efficacy of ketamine is well established in anaesthesia and has extensive applications in other specialties. Ketamine sedation facilitates potentially difficult procedures while minimising emotional trauma to distraught children. When used under proper precautions, complications of aspiration and laryngospasm are extremely rare.[77]

Both the IM and IV routes display similar risk of airway and respiratory AEs and of clinically important recovery agitation. However, the IM route is associated with a higher rate of vomiting and a longer recovery, and therefore, IV administration is preferred in settings in which venous access can be obtained rapidly with minimal upset to the child. Further, the IV route is also beneficial for extensive procedures (>20 minutes) in that it permits convenient repeated dosing. In other settings, the IM route may be preferred.

The following table summarises literature information regarding the efficacy of ketamine for paediatric procedures. A number of articles were already discussed in Section IV.3 of this report but for completeness, all the literature articles provided by the MAH are summarised below.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
Gharavifard[21]	Single blind clinical study	1.5 mg/kg IV or 4 mg/kg IM	IV and IM	Between 3 months and 15 years	240	Anaesthesia and Analgesia	Ketamine exhibited excellent and moderate efficacy in 66.7% and 32.5% in the IV group and 70.0% and 25.0% in the IM group, respectively (p = 0.02). Optimal sedation was reported for 20.6 ± 12.0 and 37.2 ± 11.8 minutes in the IV group and IM group, respectively (p<0.001).	There was no significant difference between sedative and analgesic effect of IM and IV ketamine. However, the onset of action and duration of effect were more desirable in the IV group for suturing, fracture reduction, and foreign-body removal.
Irving[15]	study	10 mg/kg	IM	Between 7 and 130 months	72	Anaesthesia	Postoperative analgesia was observed to be excellent in 92% of children. Only 2 of the 17 children received paracetamol (10-15 mg/kg) for pain.	No additional clinical benefits were observed with fentanyl plus ketamine, compared with ketamine alone.
Haque[Error! Bookmark not defined.]	Retrospective study	0.5 mg/kg	IV	Between 6 months and 14 years	124	Analgesia	All procedures were completed successfully indicating success of sedation.	Low dose ketamine and propofol were reported to be highly effective in facilitating painful procedures in paediatric population.
Begec[Error! Bookmark not defined.]	study	0.5 mg/kg	IV	Between 3 and 132 months	80	Anaesthesia	Mixing ketamine with propofol showed a success rate of 100% as compared to mixing alfentanil with propofol, which achieved a success rate of 95%.	The administration of ketamine with propofol, preserved haemodynamic stability and reduced the time to the return of spontaneous breathing during ProSeal laryngeal mask airway placement.
Erden[Error! Bookmark not defined.]	Prospective, randomised study	2 mg/kg	IV	Between 3 months and 15 years	40 (20 received ketamine, 20 received propofol/fentanyl)	Sedation and Analgesia	Procedural time and discharge time were similar in the 2 groups, whereas the recovery time was significantly longer in Group ketamine compared with Group propofol/fentanyl (p<0.05).	Midazolam premedication with ketamine and propofol/fentanyl provided efficacious sedation and analgesia during extracorporeal shockwave lithotripsy in children.
Miyamoto[Error! Bookmark not defined.]	Prospective, randomised, double-blind study	2 mg/mL ketamine or 5% glycose IV (control)	IV	Between 10 and 23 months	105	Sedation and Analgesia	Ketamine group showed lesser agitation in comparison with control group (CG; p<0.05).	The pain and discomfort due to airway narrowing in post palatoplasty was reduced by intraoperative ketamine.
Edge and Morgan[Error! B	Observational study	5 mg/kg titrated to	IM	Between 13	16	Sedation	Patients achieved adequate sedation. Supplementary ketamine	Ketamine was beneficial in providing satisfactory

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
ookmark not defined.		a maximum induction dose of 12 mg/kg		months and 7 years			was required only in 20 instances (7%) only.	sedation in children undergoing radiotherapy treatment.
Priestley[Error! B ookmark not defined.]	study	1.0-1.5 mg/kg IV or 3-4 mg/kg IM	IV and IM	Between 1.5 and 12 years	28	Analgesia	Onset of sedation was quicker in IV route (2.0 minutes) as compared to the IM route (3.7 minutes). The time to discharge following ketamine administration averaged 93.9 minutes (range: 67-145 minutes) in the IV group and 112.3 minutes (range: 78-180 minutes) in the IM group.	Ketamine sedation could be effectively used in children requiring immobilisation to perform painful procedures.
Green[89]	Prospective study	4 mg/kg	IM	Between 14 months and 13 years	108	Sedation	Fully adequate sedation, analgesia, and immobilisation were produced by a single ketamine dose alone in 93 cases. Overall parental reaction to the use of ketamine sedation was strongly positive.	Ketamine could be used effectively by emergency physicians to facilitate procedural sedation in children aged 12 months to 15 years.
Mason[Error! B ookmark not defined.]	Prospective study	1-2 mg/kg as bolus and 25-125 µg/kg/minute as infusion	IV (as bolus and as infusion)	Between 1 and 18 years	39	Sedation	Procedural success in patients without sedation failures. Average duration of all sedations was 53 minutes. The mean ketamine sedation dosage was found to be 1.5 mg/kg. On an average, recovery was established within 30 minutes.	The authors concluded that ketamine was effective in providing paediatric sedation.
Svenson[Error! B ookmark not defined.]	Retrospective study	1 mg/kg IV or 1 to 5 mg/kg IM	IV and IM	Between 2 months and 75 years	40	Sedation and Analgesia	In all burn patients, ketamine was used for pain control and sedation and had reported significant pain relief. In the cardiac patients, ketamine was used for sedation as they were hypotensive and intubated. In the asthma patients, ketamine was used for sedation. In trauma patients, most received ketamine for sedation and analgesia. In 8 patients, ketamine was used for pain control. In 3 of them, ketamine was used for pain control before extrication with or	Ketamine is an ideal drug for use in certain prehospital situations.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							without IV access; the others had significant pelvic or long bone injuries and had no relief of pain with narcotics. In 5 patients, ketamine was used as an aid to procedural sedation. In the cardiac and trauma patients, none had reported blood pressure drop following ketamine administration.	
Seigler[56]	Retrospective study	NA	IV	1 month-22 years	405	Sedation	Patients were significantly more likely to have airway or haemodynamic effects with propofol than with ketamine, although these effects were essentially minor in nature.	The authors therefore concluded that both propofol and ketamine provided effective sedation for the procedures performed.
Seol[Error! Bookmark not defined.]	Randomised study	1 mg/kg ketamine and 2 mg/kg propofol or 2 mg/kg of propofol and 0.1 µg/kg of remifentanil continuous infusion	IV	12-36 months	50	Sedation and analgesia	No significant differences were observed between the 2 groups in the drug requirements, occurrence of patient movement, surgeon's satisfaction, incidence of respiratory depression, hypoxia, or nausea and vomiting.	Propofol-ketamine and propofol-remifentanil combinations were effective for sedation and analgesia in paediatric patients undergoing burn dressing changes.
Ozyilkan[92]	Case report	1 mg/kg	IV	11 months	1	Anaesthesia		The combination of ketamine and dexmedetomidine for sedation allowed appropriate surgical conditions while providing haemodynamic stability in cardiac and pulmonary high-risk infants during emergent inguinal hernia repair.
Ustun[Error! Bookmark not defined.]	Randomised prospective study	0.5 mg/kg	IV	1 month-12 years	120	Sedation	Sedation was effective in all children and the mean total doses of thiopental and ketofol received by	Both ketamine-propofol and thiopental provided effective and safe sedation, but thiopental had a comparable

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							children were 4.9 ± 0.9 mg/kg and 2.6 ± 0.8 mg/kg, respectively.	effectiveness with shorter anaesthesia inductions and recovery time than ketamine-propofol.
Jurair[94]	Retrospective chart review	0.5-1 mg/kg	IV	6 months-16 years	3233	Sedation	The study results demonstrated a satisfactory sedation level in 3486 procedures (99%). The drug was well tolerated in the patients apart from few adverse effects including hypoxia (n = 21; 0.6%), apnoea (n = 7; 0.2%), and post-sedation hallucinations (n = 2; 0.06%).	Procedural sedation and analgesia with ketamine was safe and acceptable
Metainy[95]	Prospective, randomised, double-blind study	1-1.2 mg/kg ketamine and propofol (Group K) Or 1% to 2% sevoflurane (Group S)	IV Infusion	1 month-4 years	90	Sedation and Anaesthesia	However, Group S had a significantly shorter recovery time (p = 0.0001) and a significantly higher incidence of nausea and vomiting (0 vs 12, p = 0.000). Apnoea occurred in 2 patients of Group S in the first postoperative hour. Emergence agitation (EA) was observed in 12 patients belonging to Group S (p = 0.001). The Watcha scale for EA revealed significantly lower scores in Group K at 10 minutes postoperatively (1 [0-2] vs 3[1-4]; p = 0.001).	The propofol- ketamine combination was superior to sevoflurane because the incidence of agitation, nausea and vomiting in patients given sevoflurane was significantly higher than in the ketofol group.
Kidd[Error! Bookmark not defined.]	Retrospective review	1.25 mg/kg IV or 3.94 mg/kg IM	IV or IM	14 months-15 years	243	Sedation	No differences were seen in the mean initial doses for those patients who required additional sedation with IV (p = 0.07) or IM (p = 0.20) ketamine. AEs were noted in 9.8% of the patients. The most common AEs noted with ketamine sedation were agitation and apnoea. Both these AEs were classified as being of minor risk based on the transient nature of the events.	An emergency department paediatric ketamine sedation programme could be delivered safely in a UK non-specialist tertiary paediatric centre.
Bhimani[97]	Retrospective notes and record review	NA	NA	6 months-16 years	3042	Sedation and Analgesia	Of the total 3042 diagnostic and therapeutic procedures performed, satisfactory level of sedation was achieved in 3016 (99%) of the procedures. AEs were observed in 26 (0.85%) of patients and included	Procedural sedation and analgesia using ketamine and propofol was a safe and effective option in paediatric oncology patients at a tertiary care setting.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							13 episodes of hypoxia, 9 episodes of apnoea, and 4 episodes of post-sedation hallucination. However, no major AEs were observed.	
Ahmed[98]	Retrospective analysis	0.25-0.5 mg/kg ketamine followed by IV propofol or propofol alone	IV	6 months-18 years	754	Sedation	The mean total propofol dose requirements were significantly different between the 2 groups (0.28 ± 0.20 for ketamine-propofol group vs 0.40 ± 0.26 mg/kg/minute for propofol-only group; p<0.0001). The mean procedure time was also longer in the ketamine-propofol group (18.68 vs 15.11; p<0.01) with much shorter recovery times (17.04 vs 22.17; p<0.01) as compared with the propofol-only group.	Both propofol-only and propofol with a sub-dissociative dose of ketamine are well tolerated and effective in procedural sedation in children. The authors added that addition of low-dose ketamine was also associated with reduction in recovery time making both the approaches a viable option for procedural sedation in children.
Barr[Error! Bookmark not defined.]	Prospective study	0.5 mg/kg	IV	Mean age: 34 months	27	Sedation	The pulse rate was elevated from a normal value of 104 to 125, an increase of 20%. The mean blood pressure across all subjects during treatment was elevated 12% from the baseline (112/64). The respiration rate averaged 23 breaths per minute. Mean behaviour composite scores were 1.9 at the initial examination and 3.3 during treatment.	IV sedation of precooperative healthy paediatric patients with ketamine, fentanyl, and N2O/O2 appeared to be an effective sedation modality by providing the practitioner an alternative to general anaesthesia.
Honarmand[22]	Double-blind, randomised, placebo-controlled clinical study	IV 0.5 mg/kg ketamine (Group 1), peritonsillar infiltration of tramadol 2 mg/kg (Group 2), IV ketamine 0.5	IV	Between 2 and 15 years	120	Analgesia	There was a significant difference in the median of sedation scores between the 4 treatment groups at the time of arrival to the post-anaesthesia care unit (PACU) and 15 minutes after that (p<0.05). Patients in Groups 1 and 3 were comparatively more sedated than the patients in Groups 2 and 4 at arrival to PACU (p<0.05). The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) scores were significantly lower in Group 3 compared with others at all times till 24 hours after surgery	The combined use of IV ketamine 0.5 mg/kg with peritonsillar infiltration of tramadol 2 mg/kg provided better and more prolonged analgesic effects compared with using each drug alone.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		mg/kg added to peritonsillar tramadol 2 mg/kg (Group 3) and IV, and peritonsillar infiltration of 0.9% saline (Group 4).					($p<0.05$). Further comparison between other groups showed that the CHEOPS score was significantly lower in Group 2 compared with Group 4 till 4 hours after surgery ($p<0.05$).	
Marcus[23]	Double-blind clinical study	0.5-0.6 mg/kg ketamine or morphine 0.1 to 0.15 mg/kg	IM	Between 6 and 15 years	80	Analgesia	Both the Faces and CHEOPS pain scores were greater in the ketamine group during the first 30 minutes after extubation; however, the scores were later similar to morphine group at 1, 2, 3, and 4 hours after extubation. Rescue medicine was required by 1 patient in each group, and hence, these 2 patients were excluded from the study due to protocol violation. Additional analgesia was provided to a similar number of patients in both the groups.	Ketamine may be a useful substitute for morphine in children undergoing tonsillectomy.
Tarek Tammam[Error! Bookmark not defined.]	Double-blind study	4 mg/kg ketamine (Group K), 3 µg/kg dexmedetomidine (Group D), 1.5 µg/kg dexmedetomidine and 2	IM	Between 2 and 7 years	162	Sedation	The onset of satisfactory sedation was significantly shorter in the DK group in comparison with the D group (4.8 ± 1.6 vs 16.8 ± 4.5 minutes, $p<0.05$), while no significant difference was observed between the DK and K group (4.6 ± 1.5 minutes). The duration of sedation was significantly higher in K group compared with D and DK group (47.8 ± 4.5 vs 25.8 ± 3.6 minutes and 24.7 ± 3.1 minutes, respectively, $p = 0.030$). A	With respect to the onset of action and sedation failure rate, the combination of IM dexmedetomidine and ketamine was found to be superior to the individual drugs in paediatric MRI sedation.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		mg/kg ketamine (Group DK)					remarkably lower rate of sedation failure was reported in the DK group compared with Group K and Group D (5.6% vs 22.2% and 27.8%, respectively, p = 0.007). Also, the use of rescue midazolam was significantly lower in the DK group compared with the K and D groups (0.03 ± 0.12 vs 0.21 ± 0.41 and 0.24 ± 0.41 mg, respectively, p = 0.002).	
Safavi[24]	Randomised, double-blind, placebo-controlled study	either a single dose of dexamethasone 0.5 mg/kg IV as Group D (n = 30), ketamine 0.5 mg/kg IV as Group K (n = 30), dexamethasone 0.5 mg/kg IV and ketamine 0.5 mg/kg IV as Group KD (n = 30), or an equivalent volume of saline as Group C (n = 30) at 15	IV	Between 2 and 12 years	120	Analgesia	A significantly low observational pain score (OPS) was reported in Group KD compared with all other groups at the time of arrival to the PACU, and at 15, 30, 45, and 60 minutes and also at 1, 2, 4, 6, 12, and 24 hours after operation (p<0.05). However, OPSs were not significantly different between Group K and D. The median sedation values at any postoperative period were not significantly different among the groups. The postoperative analgesic requirement was significantly low in Group KD compared with Group C (p<0.05) and Group D or Group K (p<0.001). The time taken for first oral intake was remarkably lower in Group KD compared with other groups (p<0.05).	The use of prophylactic preoperative single dose of IV dexamethasone 0.5 mg/kg in combination with a single dose of IV ketamine 0.5 mg/kg in patients undergoing tonsillectomy reduces postoperative pain and progresses oral intake compared with the individual use of these drugs.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		minutes before the induction of anaesthesia.						
Cha[25]	Prospective, double-blind, randomised study	0.5 µg/kg/hour of fentanyl or 0.5 µg/kg/hour of fentanyl plus 0.15 mg/kg/hour of ketamine	IV	Between 6 and 16 years	60	Analgesia	A significantly lower visual analogue scale (VAS) pain scores was observed in fentanyl and ketamine group than in fentanyl group at 6, 24, and 48 hours after surgery ($p<0.05$). Additional analgesic, ketorolac was required by 7 patients in fentanyl and ketamine group compared with 18 patients in fentanyl group during 48 hours of surgery (23% vs 53%, $p<0.01$).	The addition of low-dose ketamine to fentanyl showed a considerable decrease in pain scores after Nuss procedure in paediatric patients.
Auletta[36]	study	atropine (0.01 mg/kg) and midazolam (0.05 mg/kg) over 5 minutes, followed by an infusion of ketamine (up to 2.0 mg/kg) over an additional 5 minutes.	IV Infusion	Mean age: 7.3 ± 4.4 years	69	Analgesia and Sedation	The clinical efficacy rate was observed to be 91%. No additional medication was required for further sedation or analgesia in 232 procedures, while 23 procedures (9.0%) required additional midazolam and/or ketamine.	An atropine-midazolam-ketamine regimen was as efficacious as an analgesic and sedative in the larger proportion of the patients who underwent painful oncology procedures.
Moawad[11]	Randomised, double-blind study	3 Groups of 40 each to either	IV	Between 2 and 7 years	120	Anaesthesia	A significantly lower emergency agitation (EA) score was reported in ketamine 1.0 group compared with ketamine 0.25 and saline groups	The premedication with ketamine was effective in reducing emergence agitation without delay in recovery and

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		receive normal saline, 0.25 mg/kg of ketamine IV 10 minutes prior the end of the procedure, or 1.0 mg/kg of ketamine IV before sevoflurane induction.					(2.50 ± 0.99 vs 4.63 ± 0.95 and 12.00 ± 1.59, respectively, p<0.05). Further, ketamine 0.25 group showed significantly lower EA score in comparison with saline group (4.63 ± 0.95 vs 12.00 ± 1.59, p<0.05). Patients in ketamine 1.0 group reported significantly lower incidence of pausing and interruption of MRI procedure in comparison with ketamine 0.25 and saline groups (2.5% vs 15% and 17.5%, respectively, p<0.05).	significantly reduced the frequency of pausing of MRI scan.
Thomas[12]	Double-blind, randomised study	3 groups; namely, Group A receiving ketamine 0.5 mg/kg, Group B fentanyl 2 µg/kg and Group C fentanyl 3 µg/kg at the time of induction.	IV	Between 2 and 10 years	114	Anaesthesia	The number of children who developed emergence agitation (EA) in Group B was significantly higher compared with Group A (p =0.003) and Group C (p = 0.001; 65.8% vs 31.6% and 28.9%, respectively). The necessity of rescue medication after EA was significantly higher in Group B compared with Groups A and C (65.8% vs 31.6% and 28.9%, respectively, p<0.001). Duration of anaesthesia with EA was less in Group B compared with A and C (67.08 ± 25.13 vs 80.42 ± 31.51 and 82.09 ± 31.11, respectively). Time to extubation with EA was reported to be higher in Group C compared with Groups A and B (9.09 ± 2.21 vs 7.58 ± 2.47 and 7.44 ± 2.75, respectively). Time to consciousness with EA was statistically similar between the 3 treatment groups. Duration of Post-	Ketamine 0.5 mg/kg IV or fentanyl 3 µg/kg IV administered at the time of induction reduced the incidence of emergence agitation in comparison to fentanyl 2 µg/kg, without delaying recovery.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							Anaesthesia Care Unit stay with EA was higher in Group A compared with Groups B and C (83.33 ± 5.37 vs 77.2 ± 6.14 and 76.36 ± 8.97, respectively).	
Mason[37]	Protocol in 2 phases. Aim of the first phase was to develop a sedation protocol to replace GA for specified paediatric interventional procedures.	3-6 mg/kg IM (in patients with difficulty in IV access); 0.5-1.0 mg/kg IV (for sedation shorter than 10 minutes); 1-2 mg/kg IV (for >10 minutes of sedation); 25-150 µg/kg/minute (IV infusion)	IM and IV	Mean age of 9.9 ± 8.5 years	6	Analgesia and Sedation	In phase 2, the results of phase 1 were reviewed and a formal ketamine protocol was developed. Overall, 38 patients with a mean age of 9.9 ± 8.5 years were included in the Phase 1 study. There were no failures with respect to sedation in Phase 1. All sedations occurred for a mean duration of 52 ± 28 minutes (10-120 minutes). The sedation time was longer in the patients who received ketamine through infusion than in those who received ketamine as bolus (46 ± 20 vs 28 ± 22 minutes, p = 0.02). There were no reports of prolonged sedation in any patient.	Ketamine induced sedation was found to be an effective alternative to general anaesthesia for interventional radiologic procedures in paediatric patients.
Bonneau[Error! Bookmark not defined.]	Evaluation of efficacy in paediatric oncology	NA	IV	7.4 years	48	Anaesthesia	Pain was reported to be under control during and after the procedure (89.5% Face, Legs, Activity, Cry, Consolability (FLACC) <4/10 during and 96.6% FLACC/VAS <4/10 after).	Ketamine could be used as an alternative to GA for invasive procedures in paediatric oncology.
Tamminga[14]	Double-blind, randomised	1.0-1.5 mg/kg ketamine	IV	Between 4 and 16 years	16	Anaesthesia	The pain scores were low, immediately after awakening from the ketamine anaesthesia (0 in 20 of the 32 procedures, 10 in 3, 20 in 2, and 30 in 2 others). No pain score was obtained from 5 procedures as either the patient was too sleepy or	Ketamine anaesthesia appeared as effective after diazepam premedication as after placebo premedication.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							too young. Another dose of IV ketamine (0.3-0.5 mg/kg) was required during 6 procedures to avoid the child awakening before completion of the procedure. Sudden awakening was reported by 6 children after placebo and by 1 child after diazepam premedication.	
O'Flaherty[28]	Randomised, double-blind, placebo-controlled study	4 groups of 20 each and received ketamine 0.15 mg/kg (KP group), magnesium sulphate 30 mg/kg (MP group), ketamine 0.15 mg/kg plus magnesium sulphate 30 mg/kg (KM group), or placebo (PP group) IV 5 minutes prior to the initiation	IV	Between 3 and 12 years	80	Analgesia	There was no significant difference in the postoperative pain among the groups. At discharge, all patients in all the 4 treatment groups experienced low observational pain scores. The initial sedation scores were relatively high as most of the patients were not extubated until their appearance in the PACU. A trend toward decreased sedation was observed in all the 4 groups during their PACU stay and also at discharge. Fentanyl was administered to a higher percentage of patients in the PP group compared with the patients in KP, MP, and KM group in the PACU (70% vs 50%, 40%, and 53%, respectively). However, this difference was not statistically significant. The level of pain reported at home was similar between the groups. Acetaminophen consumption in the first 24 hours was also similar between the groups. More codeine was consumed postoperatively by patients in KP and MP group compared with PP group in the first 24 hours of surgery. The PACU recovery time was similar between the 4 treatment groups (KP group: 70 ± 5 minutes, MP group: 58 ± 6 minutes, KM group: 59 ± 5 minutes, and PP group: 64 ± 5 minutes).	No decrease in pain or analgesic consumption was observed in children undergoing tonsillectomy when pre-treated with a small dose of ketamine and/or magnesium.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		of surgery						
Eghbal[30]	Double-blind, randomised study	0.25 mg/kg of ketamine (KG group, n = 33) or normal saline (CG group, n = 33)	IV	Between 5 and 15 years	66	Analgesia	Results indicated that the pain scores, the percentage of patients requiring paracetamol for postoperative pain control, and the emergence agitation were lower in the KG than the CG (p = 0.002).	IV low-dose ketamine at induction of anaesthesia may reduce postoperative pain following adenotonsillectomy, paracetamol need as a recue analgesic, and emergence agitation.
Espahbodi[17]	Randomised clinical study	Group K (ketamine, 1.5 mg/kg, fentanyl, 1 µg/kg, and atracurium, 0.5 mg/kg), Group C as CG (propofol, 2 mg/kg, fentanyl, 1 µg/kg, and atracurium, 0.5 mg/kg), and Group A (atropine, 0.15 mg/kg, propofol, 2 mg/kg, fentanyl, 1 µg/kg, and	IV	Between 4 and 10 years	90	Anaesthesia	Results indicated that the incidence of oculocardiac reflex (OCR) was 20% in the KG, 63% in the CG and 43% in the atropine group.	As ketamine was associated with a lower incidence of the OCR, it may be the better choice as an induction drug for eye surgery.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		atracurium 0.5 mg/kg).						
Inanoglu[31]	Double-blind, randomised controlled study	Group 1 (n = 30) received IV and peritonsillar saline, Group 2 (n = 30) received IV saline and peritonsillar bupivacaine, and Group 3 (n = 30) received IV 0.5 mg/kg ketamine and peritonsillar 0.25% bupivacaine (3-5 mL per tonsil).	IV	Between 2 and 12 years	90	Analgesia	The mean modified Children's Hospital of Eastern Ontario Pain Scale (mCHEOPS) score at 15 minutes, 1 and 4 hours was higher in Group 1 compared with Group 2 and at all time intervals than Group 3 ($p<0.05$). Time to first postoperative analgesic request was significantly longer in the KG than in the other groups ($p<0.05$).	IV ketamine and peritonsillar infiltration with bupivacaine were effective as part of a multimodal regime for post-tonsillectomy pain management.
Mizrak[18]	Study	1-3 mg/kg/hour ketamine (Group K) and 6-9 mg/kg/hour propofol (Group P)	IV	Between 4 and 11 years	60 (30 received ketamine)	Anaesthesia	The recovery time in Group K was lesser than that in Group P ($p = 0.008$). In Group K, the postoperative agitation score was significantly lower than in Group P ($p = 0.005$). The Face Pain Scale in Group K was considerably lower than that in Group P ($p = 0.001$). Post-surgery at 60th minute ($p = 0.02$) and during awakening ($p = 0.01$), and the Ramsay Sedation	The infusion of ketamine with fentanyl gave better anaesthesia than propofol in children undergoing strabismus surgery.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							Score was higher in Group K than in Group P.	
Care[99]	Open cohort study	propofol 1 mg/kg and ketamine 1 mg/kg, followed by maintenance dose of propofol 4 mg/kg/hour	IV	2-12 years	8	Sedation and Analgesia	The total dose of propofol and ketamine administered was 3.5 ± 1.7 mg/kg (range: 1.8-6.6) and 1.4 ± 0.9 mg/kg (range: 1-3.9), respectively. The safety level was acceptable and no unexpected side effect was reported; respiratory and cardiovascular depressions reported were mild and easily controlled; no serious AEs were reported. The recovery was quiet and of good quality in all children.	The combination of propofol and ketamine was suitable for procedural sedation and analgesia in children with burns.
Gorecha[100]	Clinical study	IV infusion containing morphine 1 mg/kg and ketamine 1 mg/kg in normal saline up to 50 mL.	IV	Average age: 8 years	19	Analgesia	The average length of stay in high-dependency unit ranged from 1 to 7 days. None of the patients had pruritus or dizziness, 1 patient had hallucinations, 1 patient had nausea, and 2 patients had vomiting.	Morphine-ketamine patient-controlled analgesia was safe and has low adverse effects.
Gulec[101]	Double-blind, randomised study	3 mg/kg ketamine; either ketamine-propofol combination (Group 1) or ketamine alone (Group 2) for induction and	IV Infusion	NA	63	Analgesia	Initial diastolic blood pressure and subsequent serial measurements at 5, 10, 15, and 20 minutes of systolic blood pressure, diastolic blood pressure, and pulse rate in Group 2 were significantly higher compared with Group 1 ($p<0.05$).	Ketamine-propofol (ketofol) combination provided better quality of sedation and haemodynamic stability than ketamine alone in paediatric circumcision surgeries.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		maintenance of sedation.						
Ahuja[102]	Prospective, randomised, and controlled, double-blind study	Group 1 received 0.25% (1 mL/kg) bupivacaine plus 0.9% (0.1 mL/kg) normal saline, Group 2 received 0.25% (1 mL/kg) bupivacaine plus 1 µg/kg fentanyl, and Group 3 received 0.25% (1 mL/kg) bupivacaine plus 0.5 mg/kg ketamine.	NA	2-10 years	60	Analgesia	The patients had achieved good pain relief with very low visual analogue scale (VAS) scores in all the 3 groups in immediate postoperative period; however, the VAS score was significantly lower ($p<0.05$) in KG compared with other 2 groups at 0.5, 1, 2, and 4 hours postoperatively. In detail, mean VAS score in bupivacaine group varied from 0.41 ± 0.51 to 2.59 ± 0.51, in the fentanyl group ranged from 0.16 ± 0.38 in immediate postoperative period to 1.74 ± 0.45 at 4 hours postoperatively, in KG it varied from 0.15 ± 0.37 in immediate postoperative period to 1.25 ± 0.72 at 4 hours postoperatively. The mean time for requirement of rescue analgesia in bupivacaine group was 4.10 ± 0.5 hours, compared with 5.95 ± 0.63 hours in fentanyl group and 8.23 ± 0.57 hours in KG ($p<0.05$). Patients in the KG were significantly more sedated than the bupivacaine group at 0.5 hour postoperatively ($p<0.05$). Sedation scores after initial 30 minutes were not significantly different between the groups ($p>0.05$).	Ketamine at a dose of 0.5 mg/kg when used as an adjuvant to bupivacaine was better than fentanyl 1 µg/kg in terms of analgesia as well as blunting of stress response.
Asadi[103]	Randomised, triple-blind, clinical study	receive 0.25 mg/kg (2 mL) IV ketamine (intervention group, n = 49) or 2	IV	3-12 years	98	Analgesia	The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) pain scales were significantly lower in the KG compared with the CG at 30 minutes (3.4 ± 1.2 and 4.04 ± 0.7, respectively, p = 0.003) and at 6 hours (2.98 ± 0.9 and 3.37 ± 0.73, respectively, p = 0.023). No significant difference was observed	The administration of IV low-dose ketamine (0.25 mg/kg) effectively reduced the pain after adenotonsillectomy, without an increased rate of AEs such as nausea, vomiting, and agitation.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		mL of IV saline 15 minutes before the end of the surgery (CG, n = 49).					in the mean of CHEOPS scale between the 2 groups at 12 hours after the surgery (2.9 ± 0.8 vs 2.9 ± 0.8, respectively). No significant difference in the dose of adjuvant analgesic (14.28% vs 22.5%, p = 0.07) and the incidence of nausea (18.4% vs 22.5%, p = 0.06) and vomiting (10.2% vs 12.2%, p = 0.07) were observed in the 2 groups postoperatively. No statistically significant difference was observed between the 2 groups in the frequency of need for rescue narcotics to control the postoperative pain (p = 0.297). No complications such as agitation, haemodynamic instability, changes in HR, respiratory distress or airway spasms, and bleeding were observed in both the groups during the first 24 hours postoperatively.	
Yenigun[104]	Randomised, controlled study	Group 1 received 0.5 mg/kg IV ketamine, Group 2 received 2 mg/kg 0.5 mg/kg rectal ketamine, Group 3 received 2 mg/kg local peritonsillar ketamine, and the CG	IV, rectal and peritonsillar	5-15 years	120	Sedation and Analgesia	No statistically significant difference was observed in the CHEOPS values between the groups measured at minutes 15, 30, and 60 minutes, as well as 2 and 12 hours (p>0.05). All the routes of infiltration of ketamine were as effective as those of tramadol hydrochloride, and a statistically significant difference was observed between IV infiltrations and all groups during the assessments at Hours 6 and 24. The analgesic efficacy of IV ketamine was observed to be higher at 6 and 24 hours (5.19 [1.03], p = 0.045 at 6 hours; 4.86 [0.91], p = 0.011 at 24 hours).	Perioperative, low-dose IV, rectal, or peritonsillar ketamine infiltration provided efficient pain relief with low incidence of adverse effects in children who underwent adenotonsillectomy.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		received 2 mg/kg IV tramadol hydrochloride infiltration.						
Minoshima[105]	Single-centre, prospective, randomised, placebo-controlled study	Either 0.5 mg/kg of ketamine as a bolus after tracheal intubation followed by continuous infusion of ketamine at a rate of 2 µg/kg/minute until 48 hours after surgery (KG, n = 17) or normal saline (placebo group, n = 19).	IV (bolus or infusion)	10-19 years	36	Sedation and Analgesia	No significant difference between groups in Numerical Rating Scale (NRS) pain scores either at rest or on motion. Sedation scores were similar between the groups. No difference in the incidence of postoperative nausea (68% vs 41%, p = 0.17) and vomiting (3, 42% vs 11%, p = 0.06) was observed in the placebo group compared with the KG, but antiemetic consumption in the 48 hours after surgery was smaller in the KG than in the placebo group (metoclopramide 5.3 ± 5.9 vs 15.8 ± 16.0 mg, p = 0.03). There was no delirium or other psychotomimetic adverse effect in both the groups.	The combination of an intraoperative and a postoperative ketamine infusion appeared to have morphine-sparing effects and to decrease antiemetic requirements in posterior correction surgery for adolescent idiopathic scoliosis without adverse side effects.
Canpolat[106]	Randomised study	Ketamine 1 mg/kg (Group K; n = 20),	IV	3-9 years	60	Sedation	The recovery time was significantly lower in Group P (8.2 ± 4.6 minutes) compared with Group KP (15.5 ± 7.1 minutes) and Group K (11.2 ±	Ketamine, propofol, and ketamine-propofol combination were effective for IV deep sedation for tooth

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		propofol 1 mg/kg (Group P; n = 20), and propofol 0.5 mg/kg plus ketamine 0.5 mg/kg (Group KP; n = 20).					5.1 minutes; p = 0.001). The surgeon's satisfaction score was also significantly high in Group KP (good in 17 patients and middle in 3 patients) compared with Group K (good in 9 patients, middle in 6 patients and bad in 5 patients) and Group P (good in 11 patients; p = 0.003 and middle in 9 patients). No significant differences were observed between the groups in terms of haemodynamic changes, HR before and after the induction, and HR at 10th minute (p>0.05). However, HR was significantly higher in Group K than in Group KP (p = 0.020) at fifth minute and the MAP values were increased compared with baseline values at fifth and 10th minutes (p = 0.007 and p = 0.019). No statistically significant differences were observed between the groups in terms of RR, end-tidal CO2 values, SpO2 values and RSS values (p>0.05) at all times. Due to higher anxious patients present in Group KP, the postoperative anxiety score was worsened when compared with Groups K and P (p = 0.006). Postoperative nausea and vomiting were reported in 7 patients of Group K, 4 of Group KP (p = 0.016), and none in Group P. Respiratory depression was observed only in 3 patients of Group P (p = 0.043), and tachycardia was observed in 1 patient in each group (p>0.05).	extraction, in non-cooperative children with severe anxiety.
Zanaty[107]	Randomised, double-blind study	nebulised ketamine solution 2 mg/kg (Group		3-6 years	60	Sedation and Analgesia	A significantly greater level of sedation at 30 minutes was observed in Group DK compared with either Group K (p = 0.003) or Group D (p = 0.009). The recovery	The combination of low-dose ketamine and dexmedetomidine produced more satisfactory sedation and provided more smooth

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		K; n = 20), nebulised dexmedetomidine solution 2 µg/kg (Group D; n = 20), and nebulised solution of dexmedetomidine 1 µg/kg plus ketamine 1 mg/kg (Group DK; n = 20).					time was significantly brief in Group DK when compared with Group K (p = 0.039) or Group D (p<0.0001). The discharge time was brief in Group DK compared with Group D (p <0.0001) with a significantly better postoperative analgesia in Group DK than Group K (p = 0.008). Children in all the 3 groups recovered spontaneous ventilation and could be tracheally extubated within 5 to 10 minutes. The haemodynamic changes, heart rate (HR), and Mean Arterial Pressure (MAP) values were significantly lower in Group D compared with baseline values and Groups K and DK at 30 minutes after administration of premedication. However, patients in Group K and Group DK showed no significant differences between baseline HR and MAP values and values at 30 minutes after administration of premedication. Postoperative hypotension and bradycardia were significantly reported in 2 patients of Group D, whereas none of the patients of Groups DK and K experienced them. Postoperative agitation (combative and disoriented) was recorded in 1 patient of Group D, in 2 patients of Group K, and in 1 patient of Group DK. A significantly lower Children and Infants Postoperative Pain Scale score was observed in Groups DK and K compared with Group D at recovery until 1 hour postoperatively (p = 0.008).	induction of general anaesthesia, than nebulised ketamine or dexmedetomidine alone, with more rapid recovery and no significant AEs.
Disel[108]	Prospective, randomised,	Either 1 µg/kg of IV	IV	7-18 years	44	Sedation	Except for 1 patient (2.3%), all of the fractures and/or joint dislocations in the patients were	Etomidate provided effective and adequate sedation in paediatric emergency

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
	single-blind study	fentanyl followed by 0.2 mg/kg of etomidate (Group 1; n = 24), or 1 mg/kg of ketamine (Group 2; n = 20).					reduced successfully (41 patients [93.2%] in the first attempt and 2 patients [4.5%] in the second attempt). The mean total doses of study drugs received by children to provide adequate sedation and analgesia were 0.25 mg/kg of etomidate and 1.30 µg/kg of fentanyl in Group 1 and 1.25 mg/kg of ketamine in Group 2. Repeated boluses were required by 11 patients in Group 1 and 7 patients in Group 2. The mean (standard deviation [SD]) recovery time for all patients was 18.0 (9.5) minutes where it was 15.8 (7.7) minutes in Group 1 compared with 20.7 (10.8) minutes in Group 2 (p>0.05). The mean (SD) post sedation observation duration for all patients was 40.5 (15.0) minutes, whereas it was 39.7 (15.2) minutes in Group 1 and 41.4 (15.0) minutes in Group 2 (p>0.05). The mean (SD) induction time in Group 1 compared with Group 2 were 4.3 (1.0) minutes and 2.2 (1.6) minutes, respectively. The mean (SD) of the deepest sedation scores was 5.1 (0.7) in Group 1 compared with 5.2 (0.5) in Group 2 (p>0.05). The ruler-marked pain recall of the patients in the etomidate group was 6.95 ± 10.09 mm, whereas it was 8.75 ± 6.12 mm in the KG (p = 0.042).	departments for procedural sedation, when compared to ketamine. However, ketamine may be preferred for reductions because of its relatively shorter induction and longer duration.
Eskander[109]	Prospective study	1.5-2 mg/kg IV, or 3-5 mg/kg IM	IV or IM	2-12 years	100	Sedation	The study results demonstrated that patients (n = 13) developed hypoxia as a result of ketamine sedation during the procedures. The incidence of hypoxia was higher during upper gastrointestinal endoscopy (14.28%) and with IM administration (15.38%) compared	Ketamine sedation was found to be safe for paediatric gastrointestinal endoscopy without co-morbidities.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							with lower gastrointestinal endoscopy (8.69%) or IV administration (8.57%), respectively (p = 0.049)	
Kannikeswaran[110]	Randomised, double-blind, prospective study	ketamine 1 (n = 58) or 1.5 (n = 57) or 2 mg/kg (n = 56) as an IV infusion for a period of 30 to 60 seconds.	IV	3-18 years	171	Sedation	11 children (8.8%) received additional ketamine dose and the re dosing was found to be higher in the 1 mg/kg group (16%; n = 8) compared with the 1.5 group (2.9%; n = 1) and 2 mg/kg group (5%; n = 2). Further, the Ramsay Sedation Scores (RSSs) and median Faces-R score were similar in all the treatment groups. The median sedation duration in 1 mg/kg treated group was 23 minutes, in 1.5 mg/kg was 24.5 minutes, and 2 mg/kg was 23 minutes. The incidences of AEs were similar in all the treated groups and included unpleasant recovery reaction and emesis.	Adequate sedation was achieved with all 3 doses of IV ketamine, and higher doses did not increase the risk of AEs or prolong the duration of sedation.
Chinta[111]	Dose-finding study	0.5-1 mg/kg	IV	2-17 years	60	Sedation	The ED(Effective dose)$_{50}$ and ED$_{95}$ of ketamine were 0.7 mg/kg in the 2 to 5 years of age group, 0.5 and 0.7 mg/kg in the 6 to 11 years of age group, and 0.6 and 0.8 mg/kg in the 12 to 17 years of age group. Further, the median sedation time with a single dose of ketamine was 25 minutes (2 to 5 years), 22.5 minutes (6 to 11 years), and 25 minutes (12 to 17 years). Ketamine sedation was well tolerated except for post-discharge vomiting in the patients (2-5 years: 32%; 6-11 years: 17%; and 12-17 years: 16%).	Rapid infusion of small doses of ketamine achieved effective brief sedation and rapid recovery.
Farrag[112]	Prospective, randomised, observer-blind study	0.25% of bupivacaine plus 0.5 mg/kg of ketamine at a	IV	3-10 years	40	Analgesia	A significant decrease in the postoperative analgesia in the Group BK compared with Group BM based on visual analogue scale (VAS) at the end of 8 hours (3.0 ± 0.9 vs 5.1 ± 1.1; p<0.001), and 12 hours (4.9 ± 0.9 vs 6.2 ± 1.3;	Caudal administration of bupivacaine-ketamine combination was effective and safe with longer postoperative analgesia in paediatric patients who

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		volume of 0.5 mL/kg (Group BK) or 0.25% of bupivacaine plus 50 mg of magnesium sulphate at a volume of 0.5 mL/kg (Group BM).					p<0.04). The duration of caudal analgesia was also significantly prolonged in the Group BK (462 ± 17.2 minutes) compared with the Group BM (398.05 ± 12.9 minutes; p<0.001). AEs reported were postoperative nausea and vomiting.	underwent inguinoscrotal operations.
Sajedi[113]	Double-blind, randomised, clinical trial	IV infusion of 0.1 mL/kg of 1 mg/mL of midazolam, or 10 mg/mL of ketamine, or a combination of 0.5 mg/mL of midazolam and 5 mg/mL of ketamine	IV infusion	6 months-6 years	90	Sedation	The heart rate was significantly increased in the midazolam group compared with the other groups. The behaviour of the child (p<0.001) and sedation (p<0.001) were observed to be improved significantly in the combination group compared with the individual treatment groups. The extubation time and the recovery time were similar in all the study groups.	Combination of midazolam and ketamine as premedication produced more deep sedation and desirable behaviour in children when compared to midazolam 0.1 mg/kg or ketamine 1 mg/kg alone.
Abdolkarimi[114]	Single-centre, prospective, randomised, double-blind, crossover clinical study	IV ketamine 1 mg/kg and midazolam 0.1 mg/kg	IV	5-15 years	57	Analgesia	The median Richmond Agitation-Sedation Scale (RASS) score was +4 in both the groups and the RASS score was not comparable between the groups at 0, 15, and 30 minutes after sedation (p = 0.45; 0.32; 0.32, respectively). There were no	IV ketamine generated a superior clinical effect and decreased pain and can be recommended as a reasonable option before oncology procedures in

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		(Group K; n = 27) or IV midazolam 0.1 mg/kg and pethidine 1 mg/kg (Group P; n = 30)					significant differences between the 2 groups with regards to heart rate, respiratory rate, and SpO_2 ($p>0.05$). However, the MAP in Group P at 10 minutes was observed to be 91.53 ± 5.39 compared with 89.83 ± 4.36 in Group K ($p<0.05$). Nausea and vomiting were observed to be more frequent in Group K than in Group P but were not statistically significant.	children suffering from cancer.
Akbulut[115]	Prospective, randomised, single-blind study	Group A: a bolus dose of IV midazolam at 0.1 mg/kg (maximum 4 mg), followed by IV ketamine at a dose of 1 mg/kg as bolus dose 2 minutes later. If adequate sedation was not achieved, ketamine 0.5 mg/kg (maximum of 2 mg/kg) was added at	IV	4-17 years	238	Analgesia	The authors observed no difference in average endoscopic procedure times between the 2 groups ($p = 0.455$). Ramsay Sedation Score (RSS) determined was also significantly higher in Group A compared with Group B (mean ± SD: 4.94 ± 1.17 vs 2.98 ± 1.88; $p<0.01$). The recovery time of Group A was also significantly higher than Group B (78.85 ± 25.47 vs 34.46 ± 14.50 minutes; $p<0.01$).	Both midazolam ketamine and fentanyl-propofol combinations provided effective sedation in children undergoing upper gastrointestinal endoscopy. However, it was observed that children were more comfortable when a combination of midazolam and ketamine was used. A wide dose safety margin of ketamine, its superior anxiolytic and analgesic effects, and the absence of associated cardiopulmonary suppressive effects of ketamine, make midazolam and ketamine combination an ideal option during upper gastrointestinal endoscopy in children.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		intervals 2 minutes. Group B received a bolus dose of IV fentanyl at 1 µg/kg, followed by IV propofol at a dose of 1 mg/kg as bolus dose 2 minutes later. Propofol 0.5 mg/kg was added at intervals 2 minutes if adequate sedation was not achieved.						
Ali[Error! Bookmark not defined.]	Prospective, randomised, and double-blind study	Group K (n = 30) received ketofol (ketamine 0.25 mg/kg and propofol), Group D	IV	3-6 years	90	Analgesia	The results showed a similar incidence of emergence agitation (EA) in Group K and Group D at T0, T10, and T20; however, the incidence of EA in both these groups was significantly lower compared with group C. At awakening (T0), EA occurred at a rate of 26% patients in the ketofol group, 16% in the dexmedetomidine	Ketofol was as effective as dexmedetomidine in preventing EA and ketofol also provided better analgesic effect with earlier recovery, when compared to control and dexmedetomidine groups.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		(n = 30) received dexmedetomidine and Group C (n = 30) received 0.9% normal saline.					group, and 90% in the CG. At T10, the incidence of EA reduced to 10% in ketofol and dexmedetomidine groups and 60% in CG. At T20, none of the patients in ketofol and dexmedetomidine groups developed EA while it occurred in 16.7% in CG. None of the patients had EA at 30 minutes after emergence. With regards to severity of the EA, it was observed that Paediatric Anaesthesia Emergence Delirium (PEAD) score in the ketofol group (10.1 ± 0.35, 9.3 ± 1.15, 7 ± 0) and in the dexmedetomidine group (10 ± 0.25, 9.1 ± 0.57, and 6.9 ± 0.57) at T0, T10, and T20, respectively, were significantly lower than the corresponding values in the CG (15.2 ± 0.8, 12 ± 1.3, 9 ± 0). However, no significant differences were seen in EA severity between the groups that received ketofol and dexmedetomidine. Both the ketofol and dexmedetomidine groups had significantly longer extubation times ($p<0.05$) compared with the CG. However, the time to extubation was much longer in the dexmedetomidine group compared with the ketofol group (12.8 ± 1.95 vs 9.08 ± 1.7 minutes, $p<0.001$). The dexmedetomidine group also had a higher sedation score (as shown by the longer time to get modified Aldrete score ≥ 9) compared with the ketofol group ($p<0.001$) and the CG ($p<0.001$). Patients who received ketofol experienced more effective analgesia in the early postoperative period than those who received dexmedetomidine (91.58 ± 12.2 vs	

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							34.1 ± 6 minutes, p<0.001); however, both ketofol and dexmedetomidine provided prolonged analgesia compared with CG (9.2 ± 2.4 minutes in group C, p<0.001).	
Chander[117]	Parallel-group, randomised, double-blind study	Subjects were randomised to the propofol-ketamine (PK) group or propofol-fentanyl group (PF) groups and received a single dose of 1 mL/10 kg of either ketamine (0.5 mg/kg) or fentanyl (1 µg/kg), respectively. Patients in both groups received propofol at a mandatory dose of 1 mg/kg, which was	IV	3-12 years	92	Sedation and Analgesia	A significantly higher number of patients in the PF group (18/45, 40%) required ≥1 additional doses of propofol in the first minute after sedation induction compared with propofol ketamine group (10/47, 21.3%); however, this difference was not statistically significant (p = 0.051; odds ratio 2.467; 95% CI: 0.984-6.18). Also, no significant differences were seen between the groups in the number of additional doses of propofol required to achieve sedation induction (p = 0.218), to achieve successful endoscope insertion (p = 0.199), in the first minute after sedation induction (p = 0.057), and for the duration of the procedure (p = 0.697). No significant differences were observed in the duration of procedure between the PF group and the propofol-ketamine group (median 4.75 vs 5.33 minutes). A total of 4 (8.9%) children in the PF group and 2 (4.3%) children in the propofol-ketamine group (p = 0.43; odds ratio 2.2; 95% CI: 0.382-12.62) needed additional doses after sedation induction to facilitate endoscope insertion because the scope could not be inserted in the first attempt because of inadequate sedation (single dose in the PF group and 2 doses in both the children in the propofol-ketamine group). No difference was noted in	Propofol-ketamine was a better option than propofol fentanyl in view of the lower incidence of propofol injection pain because both regimens are comparable in terms of propofol requirement, other AEs, and time to recovery.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		administered in aliquots of 0.5 mg/kg every 15 seconds.					the total dose of propofol needed in either of the groups (PF median 7 vs propofol-ketamine median 7 doses). It was observed that, propofol injection pain was more frequent in the PF group (60% vs 31.9%, p = 0.007) compared with the propofol-ketamine group. Also, the incidence of O_2 desaturation was slightly higher in the PF group (4/45 or 8.9%) compared with the propofol-ketamine group (3/47 or 6.5%). No significant difference in the time to recovery, and time to oral intake between either of the groups.	
Chow[118]	Retrospective analysis	Data not available	IV	Median age: 5 years 5 months	87	Sedation	10 out of 152 procedures (6.6%) were associated with acute side effects (within 2 hours) such as rashes (n = 4), nausea and vomiting (n = 3), limb tremors (n = 1), and mild headache (n = 1). All the events were considered self-limiting and none needed medical intervention.	When conducted in a tertiary centre with skilled and trained medical personnel, adequate monitoring and involvement of families, administration of ketamine-based procedural sedation and analgesia for IM botulinum toxin A can be both safe and efficacious.
Courade[119]	Prospective, multicentre, observational study	NA	IV and Oral	Median age: 15 years	38	Analgesia in refractory cancer pain	Patients were assessed for pain based on visual analogue scale (VAS), a significantly decrease in the mean pain score from Day 1 (6.7 [2.8]) to Day 3 (4.3 [3.2]; p<0.001) was observed in the overall population. A reduction in VAS scores by at least 2 points was observed in 19 patients (50%) after 48 hours of initiation of ketamine. Nine (9) patients experienced poor tolerance, but none had limiting toxicities. Opioid-sparing effect was highlighted in 4 patients, 54% of the prescribers and 47% of the patients reported that addition of ketamine was very helpful even though they	The addition of low-doses of ketamine to opioid analgesics in children suffering from refractory cancer pain reduced the intensity of pain in half of the study population.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							did not experience an improvement in their pain scores.	
Barois[26]		mean dose 1.8 ± 0.9 mg/kg	IV	Preterm newborns	57	Analgesia	In the ketamine group, the mean pain score on the validated acute pain rating scale for term and preterm neonates (APN) scale was 3.6 ± 2.5 before the tracheal intubation procedure (vs 1.1 ± 1.8 in the no analgesia group, p<0.01) and 0.4 ± 0.7 during the procedure (vs 2.9 ± 3.2 in the no analgesia group, p<0.001).	Short venous catheter insertion followed by immediate analgesia with ketamine and atropine was effective in lessening pain during tracheal intubation of preterm newborns in the delivery room.
Romanowski[27]	Matched cohort review	2-3 µg/kg/minute ketamine (KG) or standard postoperative pain control (non-KG)	IV Infusion	Data not available	22	Analgesia	The Richmond Agitation-Sedation Scale (RASS) score was −0.8 ± 0.5 vs −0.9 ± 0.7, and mean OPS was 1.0 ± 0.9 vs 1.1 ± 0.7 in the ketamine and non-KG, respectively. Difference was seen in the individual mean Observational Pain Scores (OPSs) as 8 out of the 11 patients who received ketamine had a mean pain score <1, while only 4 out of 11 in the non-KG had mean pain score <1.	The use of ketamine infusion in postoperative burn patients may help enhance the activity of pain medications.
Sareenmaa[32]	Randomised, double-blind, crossover study	Random infusions 0.5 mg/kg, 1 mg/kg and 2 mg/kg ketamine or placebo	IV	Newborn infants	16	Analgesia	The results indicated that the increase in the pain score caused by the tracheal suction from a median baseline level of 0 was significant (p = 0.001) after placebo. A similar increase was found after the ketamine doses of 0.5 mg/kg (p = 0.001) and 2 mg/kg (p = 0.004). It was only after the administration of 1 mg/kg, there was an attenuation of the pain score change found (p = 0.043) compared with placebo.	IV ketamine administered during the first few days of life had a small or moderate analgesic effect on the pain caused by endotracheal suction.
Cotsen[42]	Study	2 mg/kg IV or 3 mg/kg IM	IV or IM	3 days to 10 years	211	Interventional radiology	About 91% of patients showed excellent sedation. Transient desaturation below 95% occurred in 11 patients (5%). The airway was manipulated to improve ventilation (head, neck, and jaw lifts) and	Only minor cardiovascular changes were observed in all patients.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							supplemental O_2 was given via nasal cannula or mask. The episodes lasted only a few seconds and O_2 saturation promptly returned to a level greater than 95%.	
Pruitt[53]	Study	3 mg/kg of ketamine	IM	12 months-7 years	37	Sedation	Around 70% patients had excellent sedation, and the remaining 30% patients showed acceptable sedation. However, 5 patients required IM infusion of 1 mg/kg ketamine to complete the procedure.	It was noticed that the time to recovery ranged from 50 to 120 minutes.
Petrack, Marx, and Wright[54]	Study	4 mg/kg	IM	6 months-6 years	Data not available	Sedation	All patients experienced acceptable sedation.	The time to recovery and discharge ranged from 75 to 96 minutes.
Van Wijhe, Stricker, and Rejger[55]	Study	2.0 mg/kg	IV	4 months-17 years	68	Sedation	Postoperative recovery time ranged from 15 to 120 minutes. On an average 70% patients recovered within 30 minutes.	Ketamine can be considered effective as a paediatric dissociative anaesthetic/sedative agent.
Lauretti[41]	Study	The patients in the CG, dipyrone group (DG), KG and ketamine /dipyrone group (K/DG) were randomised to receive IV saline, 10 mg/kg dipyrone, 0.2 mg/kg ketamine	IV	NA	24	Sedation and Analgesia	Time to first request for analgesia (TFA) and number of analgesic doses used in first 24 hours were recorded. The time to first rescue analgesics (minutes) was: KG = 525 ± 341 and K/DG = 1170 ± 373 when compared to CG = 3.7 ± 0.5 and DG = 2.2 ± 1. Also, the study suggested that CG = DG<KG ($p<0.002$) <K/DG, which was statistically significant.	Pain scores at 24 hours evidenced by Visual Analogue Scale (VAS) evaluation were significantly lesser in K/DG, compared with the CG ($p<0.05$).

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
		, and 10 mg/kg dipyrone + 0.2 mg/kg ketamine , respectiv ely.						
Stevic[120]	Randomised, prospective analysis	Dosage data not available. Either IV ketamine and fentanyl (Group 1) or IV ketofol and fentanyl (Group 2)	IV	Data not available	103	Sedation and Analgesia	The results demonstrated that the pulse dye laser treatment in the Department of Plastic Surgery was completed successfully in all patients. The most commonly observed AE was nystagmus; the frequency of nystagmus was 35.5% in Group 1 compared with 5% in Group 2 ($p<0.001$). Post-procedural nausea and vomiting were more frequent in the Group 1 compared with Group 2 ($p<0.05$). No statistically significant differences between groups were observed in terms of satisfaction of parents.	The combination of ketofol and fentanyl for procedural sedation and analgesia in paediatric patients undergoing laser procedures.
Sheehy[121]	Longitudinal, observational, cohort study	0.1-0.3 mg/kg/ho ur for 4-8 hours/da y	IV Infusion	Data not available	63	Analgesia	The results demonstrated that ketamine significantly reduced the overall pain scores ($p<0.001$) and obtained greater reduction of pain scores in patients with complex regional pain syndrome (CRPS) than in patients with other chronic pain syndromes ($p = 0.029$). Further, ketamine-associated pain score reductions were greater in postural orthostatic tachycardia syndrome (POTS) and trauma patients and lowest in patients with chronic headache ($p = 0.007$). In 37% (N = 99 out of 277) of infusions, patients had a >20% reduction in pain score. The effect of ketamine treatments (1 to 3 consecutive daily infusions	Repeated infusions of ketamine were feasible and safe for the treatment of chronic pain in children and adolescents.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							amounting to a total of infusions 16 hours) on pain scores found that ketamine treatments significantly decreased the pain scores (−1.6 ± 0.24, mean change ± standard error of the mean (SEM, p<0.001). With regard to the effect of ketamine on opioid intake, after each infusion, ketamine did not change oral morphine-equivalent intake (−0.03 ± 0.031, mean change ± SEM, p = 0.3) compared with baseline doses and ketamine treatments (up to 3 daily infusions) did not reduce oral morphine-equivalent intake (−0.1 ± 0.05 mg/kg/day, p = 0.17). No psychotropic side effects, hallucinations, nausea, vomiting, or changes in sleep pattern were reported by any patient during ketamine administration.	
Barcelos[Error! Bookmark not defined.]	Randomised, clinical study	2 mg/kg ketamine up to max 70 mg or 0.1 mg/kg morphine up to max 5 mg	IV	Data not available	25	Analgesia	The results showed that both protocols were effective with no treatment failures in either group. No significant differences were seen between the 2 groups in the time to begin intervention or total procedure time. However, the duration of the intervention was significantly lower in the morphine group compared with the KG (median of 3 vs 5 minutes; p<0.027). The average time of hospitalisation was similar in both groups (ketamine = 10.8 ± 5.2 vs morphine = 12.3 ± 4.4 hours; p = 0.447). In both groups, the median pain score analysed by the Faces Pain Scale following the procedure was 2. There was no statistically significant difference between the 2 groups in the presence of pain at the end of the procedure. In both treatment	With regards to pain control, shorter start time of the intervention by the orthopaedist, lower total procedure time, success in reduction of the fracture, the presence of amnesia, and low incidence of adverse effects in particular respiratory disorders, ketamine was shown to be a safe and effective analgesic for use in orthopaedic emergencies.

Primary author	Study type	Dose (mg/kg)	Route	Age range	No. of subjects	Therapeutic use	Results	Conclusions
							groups, most of the children had no memory of the procedure (ketamine = 92.3% vs morphine = 83.3%; p = 0.904). In the KG, a higher percentage of parents (84.6%) were very satisfied with the analgesic intervention compared with the morphine group (66.6%; p = 0.296). Similarly, a higher percentage of orthopaedists expressed maximum satisfaction regarding the intervention in the KG (92.3%) compared with the morphine group (75%; p = 0.222).	

4. Guidelines

In a 2011[1] update of the 2004 Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation in children, the authors Green et al[1] recommended the following:

Ketamine Administration: IV Route

Administer a loading dose of 1.5 to 2.0 mg/kg IV in children or 1.0 mg/kg IV in adults, with this dose administered during 30 to 60 seconds. More rapid administration produces high central nervous system levels and has been associated with respiratory depression or apnoea.

Additional incremental doses of ketamine may be administered (0.5 to 1.0 mg/kg) if initial sedation is inadequate or if repeated doses are necessary to accomplish a longer procedure.

Ketamine Administration: IM Route

Administer ketamine 4 to 5 mg/kg IM in children; while the IV route is preferred for adults.

Repeat ketamine dose (full or half dose IM) if sedation is inadequate after 5 to 10 minutes (unusual) or if additional doses are required.

5. Conclusion

The efficacy of ketamine is well established based on available clinical data. Appropriate administration of ketamine results in induction of anaesthesia either alone or as a supplement to other agents while minimising emotional trauma in paediatric patients. Ketamine can be administered safely in emergencies by physicians and other HCPs to facilitate procedures in paediatric patients when used as part of a defined protocol. No lower age limit was identified for the use of ketamine in pediatric patients. With regard to the IV route, common loading doses are 1.5 to 2.0 mg/kg. With regard to the IM route doses of 4 to 5 mg/kg offer adequate sedation in children.

Ketamine does not exhibit dose-related AEs within the range of clinically administered doses under standard administration techniques. The sedation characteristics of the IV and IM routes appear comparable. Both the IM and IV routes display similar risk of airway and respiratory AEs. However, the IM route is associated with a higher rate of vomiting and a longer recovery, and therefore, IV administrations are preferred in settings in which venous access can be obtained rapidly with minimal upset to the child.

Rapporteur's comments:
The MAH has provided a significant number of literature articles describing the extensive use of ketamine in children. Based on the experience gathered thus far, ketamine appears to be a relatively safe and effective choice of anaesthetic in paediatric patients. No safety concern has become apparent from the submitted data.

The articles recapitulate the therapeutic indications of use in children:

- Ketamine can be administered as a sole IV agent to provide general anaesthesia or can be combined with other drugs. It has been reported that blood pressure and cardiac output are usually well maintained in the anaesthetic state associated with ketamine.
- Additionally, ketamine appears to be an effective adjuvant analgesic and has been used in relieving pain in various clinical situations that include co-analgesic use for intra- and postoperative pain, cancer pain, or neuropathic pain in children.
- It may also be administered either alone or in combination with other agents such as benzodiazepines for procedural sedation. It appears to be a commonly used drug in dentistry, the emergency department, dermatology, plastic procedures, and interventional radiology in children, producing a state of dissociative sedation.

The data do not indicate new therapeutic indication of use or new safety signal.
However, the MAH has proposed to update the SmPC with a new statement in Section 4.1 to clarify the age groups in which ketamine is indicated. In a number of SmPCs across EU, the dosage regimen for 'children' or 'paediatric patients' as a whole, is already specified in section 4.2. The SmPC update is further discussed in the response to Question 3.

iii. Question 3:

The MAH is requested to submit the core SmPC in English version that is used in various member states and the paediatric statements in the SmPCs of various member states in a tabulated form.

MAH response:
Ketamine is approved nationally in the following EU member states: United Kingdom, Ireland, Portugal, Spain, Belgium, Luxembourg, Finland, Norway, Sweden and Poland.

The paediatric statements in the Summary of Product Characteristics of various Member States are presented in the following Tabulated Form:

Member States	Paediatric Statements Included in the Summary of Product Characteristics
United Kingdom	**4.2 Posology and method of administration** … Adults, elderly (over 65 years) and children: For surgery in elderly patients ketamine has been shown to be suitable either alone or supplemented with other anaesthetic agents. … **5.2 Pharmacokinetic properties** … Distribution: … *Plasma ketamine peak concentrations are about 1.8 to 2.0 µg/mL at 5 minutes after an intravenous bolus injection of a 2 mg/kg dose, and about 1.7 to 2.2 µg/mL at 15 minutes after an intramuscular injection of a 6 mg/kg dose in adults and children.*
Ireland	**4.1 Therapeutic indications** … 3. For certain neurological, radiodiagnostic and therapeutic procedures in children to abolish movement. … **4.2 Posology and method of administration** … Adults, elderly (over 65 years) and children: For surgery in elderly patients ketamine has been shown to be suitable either alone or supplemented with other anaesthetic agents. … **5.2 Pharmacokinetic properties** … Distribution: … *Plasma ketamine peak concentrations are about 1.8 to 2.0 µg/mL at 5 minutes after an intravenous bolus injection of a 2 mg/kg dose, and about 1.7 to 2.2 µg/mL at 15 minutes after an intramuscular injection of a 6 mg/kg dose in adults and children.*
Portugal	**4.2 Posology and method of administration** … *Onset and duration* *…* *Intramuscular doses, from experience primarily in paediatric patients, in a range of 9 mg/kg to 13 mg/kg usually produce surgical anaesthesia within 3 to 4 minutes following injection, with the anaesthetic effect usually lasting 12 to 25 minutes.* …

Member States	Paediatric Statements Included in the Summary of Product Characteristics
Spain	**4.2 Posology and method of administration** … Paediatric population: *Intramuscular doses, from experience primarily in paediatric patients, in a range of 9 mg/kg to 13 mg/kg usually produce surgical anaesthesia within 3 to 4 minutes following injection, with the anaesthetic effect usually lasting 12 to 25 minutes.* … **5.2 Pharmacokinetic properties** … Distribution: … *Plasma ketamine peak concentrations are about 1.8 to 2.0 µg/mL at 5 minutes after an intravenous bolus injection of a 2 mg/kg dose, and about 1.7 to 2.2 µg/mL at 15 minutes after an intramuscular injection of a 6 mg/kg dose in adults and children.*
Belgium and Luxembourg	**4.2 Posology and method of administration** … Paediatric population The dosing of ketamine in both paediatric and adult patients should be individualized and titrated to the patient's requirements. Paediatric dosing is consistent with the dosing recommended for adults on a mg/kg basis. …
Finland	**5.2 Pharmacokinetic properties** … Biotransformation: Ketamine is degraded in the liver into three anaesthetically inactive metabolites. The half-life in plasma is approximately 80 minutes in adults, somewhat shorter in children.
Norway	**4.2 Posology and method of administration** … Infusion: … As monotherapy together with oxygen the dose should be 4-6 mg/kg/hour; used in combination with oxygen/nitrous oxide or diazepam 2-4 mg/kg/hour. If dilution of the solution is required, sodium chloride solution for injection 9 mg/ml may be used, e.g. in connection with single intravenous doses to children. … **5.2 Pharmacokinetic properties** … Distribution: … *Plasma ketamine peak concentrations are about 1.8 to 2.0 µg/mL at 5 minutes after an intravenous bolus injection of a 2 mg/kg dose, and about 1.7 to 2.2 µg/mL at 15 minutes after an intramuscular injection of a 6 mg/kg dose in adults and children.* … Biotransformation: … The plasma half-life is approximately 80 minutes in adults, somewhat less in children.

Member States	Paediatric Statements Included in the Summary of Product Characteristics
Sweden	**5.2 Pharmacokinetic properties** … Distribution: … *Plasma ketamine peak concentrations are about 1.8 to 2.0 µg/mL at 5 minutes after an intravenous bolus injection of a 2 mg/kg dose, and about 1.7 to 2.2 µg/mL at 15 minutes after an intramuscular injection of a 6 mg/kg dose in adults and children.* Biotransformation: The degradation of ketamine occurs in the liver. The terminal elimination plasma half-life is approximately 80 minutes for an adult and a little shorter for children.
Poland	**4.1 Therapeutic indications** … -For certain neurological, radiodiagnostic and therapeutic procedures in children to abolish movement. … **4.2 Posology and method of administration** … Adults, elderly (over 65 years) and children: For surgery in elderly patients ketamine has been shown to be suitable either alone or supplemented with other anaesthetic agents. …

The MAH has proposed the following new statement in Section 4.1 (in red font)

4.1. Therapeutic indications

Ketamine is indicated in children from birth to 18 years of age and in adults.

Ketalar is recommended:
As an anaesthetic agent for diagnostic and surgical procedures. When used by intravenous or intramuscular injection, Ketalar is best suited for short procedures. With additional doses, or by intravenous infusion, Ketalar can be used for longer procedures. If skeletal muscle relaxation is desired, a muscle relaxant should be used and respiration should be supported.

For the induction of anaesthesia prior to the administration of other general anaesthetic agents.

To supplement other anaesthetic agents.

<…>

Rapporteur's comments:
The MAH has provided a summary of the paediatric statements that are present in SmPCs of member states where ketamine is approved.
In the majority of SmPCs, information in section 4.2 already provides the posology of ketamine for 'children' or 'paediatric patients'.
The MAH has proposed a new statement in section 4.1 to clarify the specific age groups in which ketamine is indicated. This is endorsed as it is in line with the SmPC guideline 2009 which recommends that in section 4.1, *'it should be stated in which age groups the product is indicated, specifying the age limits'.*
The rapporteur recommends maintaining consistency with the statements already present in Section 4.2 and it would be sufficient to define the paediatric age groups as 'children'. Therefore, the rapporteur proposes the new text as follows:

Section 4.1 Therapeutic indications

Ketamine is indicated in children and in adults.

X. COMMENTS FROM MSS AT DAY 115

Following the circulation of the Day 90 PdAR, the rapporteur received comments from two member states who agreed with the conclusions of the rapporteur.

XI. RAPPORTEUR'S FINAL CONCLUSION AND RECOMMENDATION

The rapporteur concludes that based on the data provided as part of this European paediatric work-sharing procedure under Article 45, the benefit:risk balance of ketamine has remained unchanged for the paediatric population.
In line with the SmPC guideline 2009, the rapporteur endorses a new statement in section 4.1 to clarify the specific age groups in which ketamine is indicated, whilst it is also acknowledged that consistency will be maintained with posology statements already present in section 4.2.

Summary of outcome
The final SmPC recommendation is presented below:

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.1 Therapeutic indications
[This section should be amended to include the below wording]

Ketamine is indicated in children and in adults.

The applicant is therefore requested to submit a Type IB variation to update the SmPCs and PLs of ketamine in line with the above work-sharing recommendations within 60 days of this report.

XII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	MEDICINAL PRODUCT
Pfizer	Ketamine (Ketalar)

XIII. REFERENCES

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