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(54) Title: IMPROVED NOVEL, CLEAR, PAINLESS PREPARATION OF PROPOFOL

(57) Abstract: A clear, stable , ready to use anaesthetic composition comprising 2,6 Diisopropylphenol (Propofol); at least one analgesic and like drug and antioxidants in a solvent system and a process for preparing the same. The said solvent system is selected from water and 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and/or its derivatives in the ratio of 65:35 and cyclodextrin and its derivative and water, wherein cyclodextrin forms a complex with Propofol in a ratio of 1:1. The analgesic is selected from Lignocaine, Ketamine, Tramodol, Alfentanil, Pethidine, Ropivacaine, Bupivacaine, Ketamine and the like capable of being administered parenterally wherein ratio of Propofol: Lignocaine is 100:1 and Propofol: Ketamine is 100:5. The process for preparing the anaesthetic composition comprises mixing Propofol in solvent system for effective dissolution of Propofol followed by addition of analgesic agents and further addition of antioxidants in the desired quantity and mixing; adjusting the pH; filtering the mixture and filling in multidose vials.

IMPROVED NOVEL, CLEAR, PAINLESS PREPARATION OR PROPOFOL

This invention relates to a clear, stable, ready to use anaesthetic compositions containing 2,6 Diisopropylphenol (Propofol) and one or more Analgesic in a solvent system and a process for preparing the same.

BACKGROUND OF THE INVENTION :

Propofol is used as an anaesthetic agent for various surgical procedures for the patients requiring general anaesthesia and for induction, maintenance, sedation for ICU patients and also in various other clinical situations. "Propofol-An update on clinical use," Anaesthesiology, 81, 1005-1043. There are various prior art patents cited for the Process of formulations and its usage in Anaesthesia.

Presently various cloudy emulsions in the form of Propofol containing drug are available in the market and various patents are cited to improve such emulsion compositions either for stable homogenized formulation (WO0197779) or for its stability against microorganisms by use of addition of EDTA or addition of sulphite (US 6,399,087, US 6,469,069, CN1331582T, WO0010531, EP 1,163,007).

Further to make the solution the clear, use of surfactants like Cremophor-EL was tried, and because of anaphylactic shocks in animal, such formulation has not reached the market. It also caused pain during Anaesthesia.

US Patent 6,326,406 disclose clear injectable formulation of Anaesthetic. Subsequently other patents of various Cyclodextrin based formulations and use of lecithin were cited (Ref. WO0197796). The use of cyclodextrines has been limited because of Nephro- toxicity when administered through paranteral route . This solution on paranteral administration also causes pain.

Recently various Patents have been cited for the Prodrug formulation of Propofol viz., US 6,458,772, US 6,254,853 & W0995855. The disadvantage of such formulations are that they, when administered liberate the active moiety of Propofol and for which the anaesthetic therapy is required to be standardized.

US Patent 6,071,974 and EP 1,143,962 disclose the Process of manufacturing Propofol injections using 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol as excipient and has addressesd an advantage of preparing various concentrations of Propofol formulations, for their use in Mammals including Humans.

However all cited prior arts and preparations available in the market have exhibited phenomena of Pain during the induction of anaesthesia in 70% of the cases and is discomforting to the patient and surgeons. This phenomena is also observed to the lesser content in our cited prior art when directly administered as bolus to the humans during clinical trial. The percentage of such pain was observed in few cases, patients complaining however did not recall the pain after recovery from Anaesthesia.

The causative factor of pain experienced during administration can be because of high viscosity of the injection flowing through vein as in case of Propofol prepared in Propylene glycol. (Ref. Anaesthesia and Analgesics, Vol. 79, 939-939.8 & Vol. 75431-435). This has also resulted to irritation, thrombo phlebitis and thrombosis.

The presently available marketed emulsion solution also induces substantial irritation and pain as seen in 70% cases of the patients(Ref. Bandolier Library through Internet) administered with the same. (also Ref. PDR 1999, page 3416 through AU Patent 6,689,601), Ref. Mirakhav R.K. (1988) "Induction Characteristic of Propofol in children: Comparison with thiopentone, "Anaesthesia 43,593–598; Stark R.D. Binks, S.M Dukta, V. N., O'Connor, K.M. Amstein, M.J.A., Glen, J.B. (1985)"A review of the safety and tolerance of Propofol ('Diprivan'), "Postgrad. Med. J., 61 S, 152-156; and Mangar, D. Holak, E.J.(1992)" Even with a low dose of Propofol administered for sedation, the incidence of pain can be high; Ref. White, P.F. and Negus, J.B. (1991)"Sedative infusions during local and regional anaesthesia: A comparison of midazolam and Propofol,"J. Clin. Anesth., 3,32-39; and Ghouri, A.F., Ramirez Ruiz, M.A., and White, P.F. (1994)"Effect of flumazenil on recovery after midazolam and Propofol sedation,"anesthesiology, 81, 335-339.

In all such above citations, authors has suggested that mechanisms responsible for venous pain on Propofol administration are unknown and no measurable reduction in pain was

detected clinically after a change from Cremaphor EL based formulation to the currently marketed Soybean oil and lecithin based formulation; Ref:, Mirakhur, R.K. (1988), Stark et al. (1985), Mangar and Holak (1992), White and Negus (1991), and Ghouri et al. (1994).

Pain is a provocative word, what causes have developed in each individual is a complex interaction between physical, genetic, psychological and mental state and depends upon experience and perception which an unpleasant sensation and not a nice one.

Further the pain factor was again debated and suggested to be because of concentration of Propofol in aqueous medium Ref. Smith, I., White, P.F., Nathanson, M & Gouldson R.(1994) "Propofol-An update on its clinical use. "Anaesthesiology, 81, 1005 – 1043.

It is also seen that, combination of carrier in emulsion when mixed with Propofol causes pain and carrier alone does not cause the pain (Ref. Pain on injection of Propofol with or without infusion of carrier fluid., E. Liljeroth, A. Grauers etal, Acta Anaesthesiol Scand 2001;45:839-841).

Earlier during use of emulsion, reduction of pain was tried by changing the catheter size or by changing the speed of injection , cooling/warming of Propofol emulsion but these were all gimmicks leading to no certainty.

Various composition in fat emulsion was modified to over come this problem with the use of medium-chain triglycerides (MCT) and long-chain triglycerides (LCT) thereby reducing free Propofol in aqueous medium. Ref. Approach to reducing pain on Injection of Propofol . Eur. Hospital of Pharmacy, 1, 15 – 21 and Doenicke, A.W. Babl, J. Kellermann, W. Rau J., and Roizen, M.F. (1996) "Reducing pain during Propofol Injection the role of the solvent,"Anaesth. Analg., 82, 472-4.

However above formulation requires use of high amount of oil and the use of high concentration of oil, may lead to difficulties in patients suffering from hyperlipidemia.. US Patent 6,071,974 and EP 1,143,962 deal with a composition which contains 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol, which is slightly oily in nature might as well cause slight pain.

Further Pain reduction in part was resolved and overcome by use of Analgesic agents administered before the induction of Anaesthesia. The use of pre-mixing 1 ml of Lignocaine 2% solution, with 9 ml of 1% Propofol during the induction of anaesthesia has shown a drastic reduction in pain (Ref.Anesth. Analg., April 1, 2000; 90(4): 989 – 992).

The disadvantage of premedication with Lignocaine given with a tourniquet 30 – 120 seconds before Propofol Injection was an effective intervention however results of pain reduction varied separately injecting Lignocaine and Propofol and pre- mixing Propofol with Lidocaine for pain reduction Ref:P Picard, MR Tramer. Prevention of Pain on injection with Propofol: a quantitative systematic review. Anesthesia and Analgesia 2000 90:963-969. Tourniquet at 50 mm Hg followed by intravenous lidocaine diminishes hand pain associated with Propofol injection, "Anesth. Analg., 74,250-252.

However, premixing has a limitations and Physician has to premix the mixture by cumbersome procedure of breaking the ampoule or withdrawal from separate Vials of Lignocaine and then mixing in appropriate dosage along with Propofol emulsion.

Various other compounds used during pain reducing intervention has given good results, like use of Pethidine, Tramadol, Ondansetron etc. (Ref. Propofol -Sodium Thiopental Admixture reduces the pain on injection, Acta Anaesthesiol. Sin 38 : 9 – 13, 2000 by Yi-Chuan Kau et al, Ref. "One year Randomized Clinical trial to compare the effect of pretreatment of Ketamine and Lignocaine on Propofol Injection Pain" by Dr. Hanumanathappa V. Airani et al, through Internet).

There are other methodologies like pretreatment with topical 60% Lidocaine tape reduced the incidence of pain (Ref. Pub-Med. Pretreatment with topical 60% Lidocaine tape reduces pain on injection of Propofol by Yokota S. et al. Dept. of Anaesthesiology, Nagoya University School of Medicine, Japan).

Intramuscular . use of injection of Lignocaine and Bupivacaine separately has also been tried for the relief of Pain caused due to Propofol Anaesthesia..

Thus it may be seen that even though various means are tried to overcome the management of pain no prior art teaches or hints for , ready to use injection available with analgesic. Thus there is a consistent need to have formulation which can overcome not only management of pain beneficial to the patients but also useful without causing any difficulties in use for the physician or surgeon

Therefore , there is a continuous need for formulation which is pharmaceutically acceptable, effective and meets patient compliance for the reduction in pain and useful for the Surgeons undertaking various surgeries.

Patent, JP 2002179562, as an abstract hints for stable premix formulation of fat emulsion process showing stability in the range of 3.0 to 6.5 in the presence of stabilizer but total disclosure is not available due to lack of English version and does not hint at clear premixed solution of Propofol with Analgesics.

It has been shown that the premix of Propofol and analgesics in emulsions result in solutions which may be stable according to the analgesic used. Thus with lidocaine the concentration of Propofol diminishes while with ketamine it is maintained for 24 hours. The change of Propofol concentration occurs during the time course in the Lidocaine Propofol mixture. (Ref. Ho-Yeong Kil M.D et al., Dept. of Anaesthesiology Seol, Korea). However this art is silent on the occurrence of phase separation in emulsions.

This shows that Propofol undergoes degradation when mixed with Lidocaine over a period of time (degradation up to 50% in 24 hrs. as formulation decomposes).

All the above difficulties are related to stability of formulations because of pH and concentration dependence of Analgesics (see JP 2002179562).

The known compositions are available as emulsions and as cocktail to oil, egg phospholipid and glycerin in water. This media is very rich source of Carbon, Hydrogen and Nitrogen. It allows the growth of microorganism and hence, almost all the cited prior arts have mentioned

how to prevent the growth of microorganisms in such formulations. Secondly this emulsion being a opaque, becomes difficult for the anesthetist for dosing. Further, such preparation of emulsion involves high technology for the preparation of formulation and once the vial or ampoule is opened it has to be consumed immediately and the product monograph also suggest not to use the vials or ampoules after certain hours .It may be further noted that it cannot be administered to the patient suffering from hyperlipidemia because of the incorporation of the fat in the formulation. Such injection also requires aseptic technology during the administration of injections because it is prone to Bio-burden.

Therefore there is a need for a Propofol injection in combination with an analgesic which is in the form of a clear solution and which is lipid free, stable and is painless on administration.

The applicants have found that Propofol based formulations in the form of a clear solution comprising an analgesic component may be formulated in solvent system. The said formulation can be administered in patients relatively with no pain.

Thus the main object of the present invention is to provide a formulation of Propofol, an analgesic component and antioxidants in a solvent system which is in the form of a clear solution and which is stable over a period of about six months or higher, cost effective, easy to administer and relatively pain free.

Another object of the invention is to provide a method of preparation of the said formulation.

Another object of the invention is to provide a formulation which is stable in the pH range of 5.0 to 7.0.

A further object of the invention is to provide a formulation that is available in the multidose vials which can be preserved at the room temperature even after multiple puncturing and still maintaining potency, biological effecacy and all other attributes of the formulation up to the end of shelf life.

Another object of the invention is that such injections can be conveniently prepared by conventional injection manufacturing procedure.

SUMMARY OF THE INVENTION

Thus according to the main aspect of the present invention there is provided a ready to use stable anesthetic composition in the form of a clear solution comprising (i) Propofol, (ii) at least one analgesic and like drug (iii) antioxidants, all being in a solvent system selected from (a) water and 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and/or its derivatives (b) cyclodextrin and its derivative and water wherein cyclodextrin forms a complex with Propofol

According to another aspect of the present invention there is provided a process for preparation of ready to use stable anaesthetic composition in the form of a clear solution comprising (i) Propofol, (ii) at least one analgesic and like drug (iii) antioxidants, all being in a solvent system selected from (a) water and 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and/or its derivatives (b) cyclodextrin and its derivative and water wherein cyclodextrin forms a complex with Propofol comprising the steps of:

(i) mixing Propofol in solvent system for effective dissolution of Propofol followed by addition of analgesic agents and further addition of antioxidants in the desired quantity and mixing;
(ii) adjusting the pH
(iii) filtering the mixture
(iv) filling in multidose vials

DETAILED DESCRIPTION OF THE INVENTION

The clear solution according to the invention is a sedative hypnotic agent used for induction and maintenance of anesthesia to mammals including humans. The composition according to the invention is an effective anaesthetic which is useful for alleviation of the pain and is still, user-friendly for the physician and doctor and is economically beneficial.

According to a preferred aspect the solvent system comprising water and 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and other alkyl derivative dissolves the lipophilic drug Propofol and antioxidant into a clear solution form and which is well tolerated, having elicited safety through toxicity studies. Various alkyl derivatives of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol may be used in the solvent system.

In this solvent system water functions as a co-solvent with 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and the concentration may vary from 30% to 70%. The standards should meet the specification of Pharmacopoeial requirements.

The Propofol concentration may vary from 1% to 3% w/v and the ratio of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol: water may be from 70 to 30 : 30 to 70. Preferred ratio of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol : water is about 65 : 35.

According to a further preferred aspect the solvent system selected is matrix of cyclodextrin and its derivatives and water, wherein Propofol being complexed with cyclodextrin and cyclodextrin and Propofol is in ratio of 1:3 , preferably 1:1.

The antioxidants are selected from the group of Tocopherols especially Alpha Tocopherol.

The analgesics and like drugs that are selected from Lignocaine, (base & hydrochloride), Tramadol, Ketorolac, Ketamine, Alfentanil, Pethidine, Bupivacaine, Ropivacaine and other analgesics that can be administered paranterally. The preferred analgesics that are used are Lignocaine, Tramadol, Ketorolac, Ketamine, Alfentanil.

The ratio of Propofol : Lignocaine in the composition is in the range of 10: 1 to 300:1, preferably 100:1 while that for Propofol: Ketamine is in the range of !0: 5 to 300:5, preferably 100:5 as the case may be.

The concentration of Lignocaine in the composition is between 0.001% to 0.1% and preferably about 0.01%.

The concentration of Ketamine is in the range of 0.001 to 0.10% preferably 0.05%.

The concentration of Tramadol is in the range of 0.01% to 0.05%.
The concentration of Fentanyl is in the range of 0.001% to 0.0015%.

The concentration of Alfentanil is in the range of 0.001% to 0.005%.

The concentration of Pethidine is in the range of 0.010% to 0.05% preferably 0.042%.

The antioxidant is selected from Vitamin E group and is present in the composition in amounts of between 0.01% to 0.2%. Alpha tocopherol is the preferred Vitamin E compound being present in the range of 0.05 to 0.1%.

The composition is made by mixing Propofol to the solvent system comprising water and 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and/or derivatives thereof so as to dissolve Propofol. To this solution the other components like Antioxidants and Analgesic agents are added in the desired levels. The pH of the solution is adjusted to between 5.0 to 7.0. The solution thus prepared is filtered and packaged appropriately.

The pH is preferably maintained at about 6.4. The filtration is carried out aseptically through Nylon 66, 0.2μ membrane filter and filled in ampoules or multidose vials under hermetic conditions and sealed with non toxic, non reactive rubber stopper and followed by sealing with aluminium cap and dispensed after quality check. Other conventional forms of packagings may also be used.

Where cyclodextrin solvent system is used, Propofol is mixed with cyclodextrin in a ratio of 1:1 to form a complex. The said complex is dissolved in water and analgesics and antoxidants are then added and mixed.

The invention will now be described in greater details and demonstrated with the help of the examples and tables.

Example 1

5.6 mmol of Propofol is taken in a round bottom flask containing 70 ml of mixture of 65 : 35 in 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and water filled with assemblance of stirring facility and side arm for flushing Nitrogen and for addition to be carried out. 0.232 mole of Alpha Tocopherol is added, subsequetly followed by addition of 0.0346 mmol of Lignocaine. The solution is stirred thoroughly under hermatic condition to dissolve the material and pH is adjusted to 6.0 – 6.5 with acid or alkali and made to volume with 65 : 35 mixture of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol : Water. Mixture is filtered through 0.22 μ, Nylon 66 filter by aseptic filtration, flushing Nitrogen and then filled in ampoules or multidose vials with butylated rubber cork on it and sealed with aluminium cap and sterilized.

Example 2

11.2 mmol of Propofol is taken in a round bottom flask containing 70 ml of mixture of 65 : 35 in 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and water filled with assemblance of stirring facility and side arm for flushing Nitrogen and for addition to be carried out 0.232 mole of Alpha Tocopherol is added, subsequetly followed by addition of 0.0346 mmol of Lignocaine. The solution is stirred thoroughly under hermatic condition to dissolve the material and pH adjusted to 6.0 – 6.5 with acid or alkali made to volume with 65 : 35 mixture of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol: Water mixture filtered through 0.22 μ, Nylon 66 filter through aseptic filtration, flushing under Nitrogen and then filled in ampoules or multidose vials with butylated rubber cork on it and sealed with aluminium cap and sterilized.

Example 3

16.8 mmol of Propofol is taken in a round bottom flask containing 70 ml of mixture of 65 : 35 in 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and water filled with assemblance of stirring facility and side arm for flushing Nitrogen and for addition to be carried out 0.232 mole of Alpha Tocopherol is added, subsequetly followed by addition of 0.0346 m mole of Lignocaine. The solution is stirred thoroughly under hermatic condition to dissolve the material and pH adjusted to 6.0 – 6.5 with acid or alkali made to volume with 65 : 35 mixture of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol: Water mixture filtered through 0.22

μ, Nylon 66 filter through aseptic filtration, flushing under Nitrogen and then filled in ampoules or multidose vials with butylated rubber cork on it and sealed with aluminium cap and sterilized.

Example 4

5.6 mmol of Propofol is taken in a 3 armed round bottom flask containing 70 ml mixture of 65 : 35, 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and Water, stirred well to dissolve and 0.232 mole of Alpha Tocopherol is added followed by addition of 0.210 m mole of Ketamine. The material is dissolved with continuous stirring for half an hour under Nitrogen. pH adjusted to 6.0 to 6.5 and dilute up to the volume of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol : Water mixture and filter aseptically through 0.2 μ Nylon 66 filter and fill the same in ampoule or vials with bromobutylated rubber stopper and sealed with aluminium cap and sterilized.

Example 5

11.2 mmol of Propofol is taken in a 3 armed round bottom flask containing 70 ml mixture of 65 : 35, 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and Water, stirred well to dissolve and 0.232 mole of Alpha Tocopherol is added followed by addition of 0.210 mmol of Ketamine. The material is dissolved with continuous stirring for half an hour under Nitrogen. pH adjusted to 6.0 to 6.5 and dilute up to the volume of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol : Water mixture and filter aseptically through 0.2 μ Nylon 66 filter and fill the same in ampoule or vials with bromobutylated rubber stopper and sealed with aluminium cap and sterilized.

Example 6

16.8 mmol of Propofol is taken in a 3 armed round bottom flask containing 70 ml mixture of 65 : 35, 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and Water, stirred well to dissolve and 0.232 mole of Alpha Tocopherol is added followed by addition of 0.210 mmol of Ketamine. The material is dissolved with continuous stirring for half an hour under Nitrogen. pH adjusted to 6.0 to 6.5 and dilute up to the volume of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol : Water mixture and filter aseptically through 0.2 μ Nylon 66 filter and

fill the same in ampoule or vials with bromobutylated rubber stopper and sealed with aluminium cap and sterilized.

Assessment of efficacy of composition according to the invention in Rat models

In order to assess the Efficacy of the Injection following dosage of prepared injection from Example 1 and Example 4 was injected in the caudal vein of Rats.

5 male Sprague Dawley Rats (100 g) were used for each group and Propofol was administered at the dose of 16.66 mg/kg.

Control was Propofol injection containing solution without Lignocaine or Ketamine.

The comparison of Anaesthetic activity is carried out. The measurement of anaesthetic activity is seen by loss of righting reflex/consciousness and the recovery time in terms of head lift. The injections were compared for observing the Pain by any noticeable irritation effect This is observed macroscopically for pain or phlebitis like oedema and erythema.

Score

No pain → -

Mild → +

Moderate → ++

Severe → +++

Efficacy study:

Control: Propofol Injection (10 mg/ml) without Analgesic

Dose	Control No	Loss of Righting Reflexes (Time)	Time of Recovery (Head Lift)	Pain
16.66 mg/kg	1	45 secs.	30 mins.	++
	2	60 secs	24 mins.	++
	3	43 secs.	25 mins.	++
	4	50 secs.	28 mins.	++
	5	75 secs.	22 mins.	+++
Mean		45.5 secs.	25.8 mins.	elicitation by irritation and erythema

Efficacy Study :

Test Solution : solution prepared by Example 1 - Propofol injection (10 mg/ml) containing 0.01% Lignocaine :

Dose	Loss of Righting Reflex	Time of Recovery	Pain
16.66 mg/kg	33 secs.	44 mins.	-
	23 secs.	40 mins.	-
	25 secs.	46 mins.	-
	30 secs.	49 mins.	-
	32 secs.	56 mins.	-
Mean	28.6 secs.	47 mins.	Nil Irritation or oedema

Test Solution: solution prepared by Example 4 - Propofol injection (10 mg/ml) containing 0.05% Ketamine

Dose	Loss of Righting Reflex	Time of Rercovery	Pain
16.66 mg/kg	28secs.	65 mins.	-
	25 secs.	64 mins.	-
	34 secs.	73 mins.	-
	23 secs.	70 mins.	-
	22 secs.	65 mins.	-
Mean	26.4 secs.	67.4 mins.	Nil Irritation or oedema

From the above results it is explicitly understood that the dose required for the injection with Ketamine and Lignocaine by the inventive process does not lead to any Irritancy or Pain at the site of injection and the equivalent dose causes more sedation than the drug containing Propofol alone. As the time require for the recovery is longer than the additional drugs, the dose of such injection will be less to achieve same recovery time.

In addition efficacy of individual formulation of Propofol injection, Lignocaine injection and Ketamine injection is carried out and the results are as follows :

Anaesthetic activity					Analgesic activity (Pain/Irritation)				
		Propofol 10 mg	Lignocaine 0.1 mg	Ketamine 0.5 mg			Propofol 10 mg	Lignocaine 0.1 mg	Ketamine 0.5 mg
Dose	No.	Loss of righting reflex	Loss of righting reflex	No Loss of righting reflex, but drowsiness	Dose	No.	Pain/Irrit-ation	Pain/Irrit-ation	Pain/Irrit-ation
20 mg/kg	1	10 secs.	No Anaesthesia	55 secs.	20 mg/kg	1	++	+	-
	2	15 secs.	No Anaesthesia	69 secs.		2	++	+/-	-
	3	9 secs.	No Anaesthesia	75 secs		3	++	+/-	-
	4	10 secs.	No Anaesthesia	120 secs		4	++	+	-
	5	8 secs.	No Anaesthesia	100 secs		5	++	+	-
	6	7 secs.	No Anaesthesia	90 secs		6	++	+	-
Mean		9.83 secs.		84.83 secs.					

Score

Mild → +

Moderate → ++

Severe → +++

Difficult to judge,

slight redness → +/-

From the above result it is evident that Propofol in isolation at the dose level stated may show Anaesthetic activity but does not show Analgesic activity.

The Anaesthetic activity is not exhibited by the Lignocaine in isolation at the prescribed dose level.

There was no Anaesthesia but drowsiness caused in Ketamine at the prescribed dose level.

The Analgesic activity is not exhibited by Propofol alone and there is a phenomena of pain. However, this is reduced to NIL level when combined with Lignocaine or Ketamine. The addition of Lignocaine and Ketamine helps in the reduction of pain immediately and there is no phase separation in our clear solution.

The Anaesthetic activity at the prescribed dose level is almost absent in the Lignocaine Injection. The Analgesic activity is seen in the Ketamine injection.

This indicates that the formulation of present invention with both anaesthesia and analgesic in the wt/wt ratio of 100 : 1 for Propofol: Lignocaine and 100 : 5 of Propofol : Ketamine provides enhanced efficacy of both anaesthesia and analgesic activity compared to anaesthesia and analgesic taken alone. It is due to the synergy between the active components in the solvent system the said activities are enhanced.

Further stability of the injections were tested for the Propofol content by stability indicating HPLC method.

Stability of Propofol Injection 10 mg/ml containing Lignocaine 0.01% solution prepared by Example 1

Test	Initial	1 month	2 months	3 months	6 months
Propofol	100.2%	100.11%	100.1%	100.15%	100.13%
Identification of Lignocaine	Passes	Passes	Passes	Passes	Passes

Stability of Propofol Injection 20 mg/ml containing Lignocaine 0.01% solution prepared by Example 2

Test	Initial	1 month	2 months	3 months	6 months
Propofol	99.97%	99.95%	99.9%	99.03%	99.00%
Identification of Lignocaine	Passes	Passes	Passes	Passes	Passes

Stability of Propofol Injection 30 mg/ml containing Lignocaine 0.01% solution prepared by Example 3

Test	Initial	1 month	2 months	3 months	6 months
Propofol	101.2%	101.11%	100.91%	100.90%	100.87%
Identification of Lignocaine	Passes	Passes	Passes	Passes	Passes

Stability of Propofol Injection 10 mg/ml containing Ketamine 0.05% solution prepared by Example 4

Test	Initial	1 month	2 months	3 months	6 months
Propofol	99.66%	99.35%	99.22%	99.31%	99.3%
Identification of Ketamine	Passes	Passes	Passes	Passes	Passes

Stability of Propofol Injection 20 mg/ml containing Ketamine 0.05% solution prepared by Example 5

Test	Initial	1 month	2 months	3 months	6 months
Propofol	100.3%	99.97%	99.935%	99.91%	99.9%
Identification of Ketamine	Passes	Passes	Passes	Passes	Passes

Stability of Propofol Injection 30 mg/ml containing Ketamine 0.05% solution prepared by Example 6

Test	Initial	1 month	2 months	3 months	6 months
Propofol	102.1%	101.9%	101.7%	101.69%	101.57%
Identification of Ketamine	Passes	Passes	Passes	Passes	Passes

The above results exhibit that there is no decomposition of Propofol content when tested by Stability indicating HPLC method as against the published prior art literature showing the

degradation. (Ref. The changes of Propofol concentration with time course in Lignocaine – Propofol or Ketamine – Propofol mixture).

HPLC METHOD :

Column A	:	Merck Lichrocant C18 purofser 250cm x 4mm S.S. Column
Mobile Phase	:	Acetonitrile (HPLC grade) : Water (HPLC grade) 70 : 30
		pH adjusted to 4.0 with Glacial Acetic Acid
Flow rate	:	1.5 ml/min
Wave length	:	270 nm
Volume of Injection	:	20 Microlitre
Sample preparation	:	Injection equivalent to 20mg of drug diluted to 100 ml with mobile phase
Standard preparation	:	20 mg of Propofol diluted to 100 ml with mobile phase.
Procedure	:	Separately inject equal volumes (20 microlitres) of standard preparation and the Assay preparation into chromatograph, record the chromatograms, and measure the responses for the major peak. Calculate the quantity in mg/ml.
Calculation	:	$\frac{\text{Area of sample}}{\text{Area of Std.}} \times \frac{\text{Dilution of Std.}}{\text{Dilution of sample}} \times \frac{\text{\% Potency of ws}}{100}$
Assay limit	:	90% - 110%

Example 7

A solution containing mixture of Lignocaine in emulsion formulation in the ratio of 100 : 1 of Propofol : Lignocaine and is prepared by conventional method of premixing comprising of 100ml of 1% solution of emulsion preparation is taken and 10 mg of Lignocaine is added shaken well to ensure the solubility . The solution is mixed and shaken well. This is compared with the composition of the present invention containing Propofol : Lignocaine prepared by mixing 1000mg of Propofol in the mixture of 2,5 di-omethyl-1,4;3,6-dianhydro-

D-glucitol and water (65:35) containing vitamin E and 10 mg of Lignocaine is added shaken well and diluted with mixture as given in the examples above in the same ratio of 100:1. The formulation was evaluated for the stability of Propofol and for the comparison of element of pain .The Anaesthetic and Analgesic activity was carried out in the Sprague Dawley Rat by administering the injection intravenously. The element of pain was observed by noticeable irritation, oedema or erythema at the site of injection and is graded.

The results are illustrated in table below:

Emulsion Formulation					Clear Formulation				
Propofol : Lignocaine 100 : 1					**Propofol : Lignocaine 100 : 1**				
Anaesthetic/Analgesic in the Animal Model					Anaesthetic/Analgesic in the Animal Model				
Dose	Control No.	Loss of righting reflex	Time of Recovery (Head Lift)	Pain	Dose	Control No.	Loss of righting reflex	Time of Recovery (Head Lift)	Pain
16.66 mg/kg	**1**	**49 secs.**	**15 mins.**	+++	16.66 mg/kg	**1**	**30 secs.**	**30 mins.**	**NIL**
	2	**53 secs.**	**22 mins..**	++		**2**	**39 secs.**	**29 mins.**	**NIL**
	3	**67 secs.**	**21 mins.**	+++		**3**	**41 secs.**	**43 mins.**	**NIL**
	4	**79 secs.**	**20 mins.**	+++		**4**	**43 secs.**	**27 mins.**	**NIL**
	5	**54 secs.**	**35 mins.**	+++		**5**	**30 secs.**	**49 mins.**	**NIL**
	6	**60 secs.**	**33 mins.**	+		**6**	**25 secs.**	**43 mins.**	**NIL**
Mean		**60.33 secs.**	**24.33 mins.**	**Elicitation by irritation or oedema/erythema**	Mean		**34.66 secs.**	**36.8 mins.**	**Elicitation by No irritation or oedema/erythema**

Score
Mild → +
Moderate → ++
Severe → +++

STABILITY STUDIES

Emulsion Formulation					Clear Formulation				
Test	Initial	1 month	2 months	3 months	Test	Initial	1 month	2 months	3 months
Description, Physical Observation	**Milky emulsion solution**	**Slightly yellow with some separation of oily layer**	**Dark yellow and floating oil**	**Dark yellow and floating oil**	Description, Physical Observation	**Clear solution**	**Clear solution**	**Clear solution**	**Clear solution**
Assay for Propofol content	**100.3%**	**93.7%**	**90.87%**	**87.7%**	Assay for Propofol content	**100.1%**	**99.9%**	**99.67%**	**99.1%**

The above results indicate that Propofol and analgesic(Lignocaine) in the ratio of 100 : 1 present in the composition of present invention forms a stable formulation without loss of potency and with good anaesthetic activity as surmised from loss of righting reflexes and time of recovery and without pain/irritation. On the other hand the premixed Propofol with analgesics in emulsion injection shows change in physical texture, with loss of potency and causing substantial irritation. This clearly indicates the superiority of the composition according to the present invention in terms of efficacy as well as stability of forms over emulsion form using the anaesthetic and analgesic in the same ratio.

Example 8

A solution containing mixture of Ketamine in emulsion formulation in the ratio of 100 : 5 of Propofol : Ketamine is prepared by conventional method of premixing 10 ml of emulsion is mixed with 5 mg of Ketamine shaken well to ensure proper mixing This is compared with the composition of the present invention containing Propofol : Ketamine in the ratio of 100 : 5 prepared by mixing 100mg of Propofol in10 ml mixture of 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and water (65:35) containing vitamin E and adding 5 mg of Ketamine to the same. Mixing it well to ensure homogenicity The stability studies were carried out for the Assay of Ketamine content. The Anaesthetic and Analgesic activity was carried out in the Sprague Dawley Rat by administering the injection intravenously. The element of Pain was observed by noticeable irritation, oedema or erythema at the site of injection and is graded.

The results are illustrated in table below:

Emulsion Formulation					Clear Formulation				
Propofol : Ketamine 100 : 5					**Propofol : Ketamine 100 : 5**				
Anaesthetic/Analgesic in the Animal Model					Anaesthetic/Analgesic in the Animal Model				
Dose	Control No.	Loss of righting reflex	Time of Recovery (Head Lift)	Pain	Dose	Control No.	Loss of righting reflex	Time of Recovery (Head Lift)	Pain
16.66 mg/kg	**1**	**49 secs.**	**28 mins.**	+++	16.66 mg/kg	**1**	**23 secs.**	**40 mins.**	**NIL**
	2	**50 secs.**	**35 mins.**	+++		**2**	**35 secs.**	**27 mins.**	**NIL**
	3	**43 secs.**	**27 mins.**	+++		**3**	**27 secs.**	**43 mins.**	**NIL**
	4	**57 secs.**	**45 mins**	+++		**4**	**29 secs.**	**23 mins.**	**NIL**
	5	**63 secs.**	**33 mins.**	+++		**5**	**31 secs.**	**20 mins**	**NIL**
	6	**65 secs.**	**63 mins.**	+++		**6**	**43 secs.**	**35 mins.**	**NIL**
Mean		**54.5 secs.**	**33.83 mins.**	**Elicitation by irritation or oedma/erythema**	Mean		**31.33 secs.**	**31.33 mins.**	**Elicitation by No irritation or oedma/erythema**

Score

Severe → +++

STABILITY STUDIES

Emulsion Formulation					Clear Formulation				
Test	Initial	1 month	2 months	3 months	Test	Initial	1 month	2 months	3 months
Description, Physical Observation	**Separation of the phases. Oily globules floating**	**Separation of the phases. Oily globules floating**	**Separation of the phases. Oily globules floating**	**Separation of the phases. Oily globules floating**	Description, Physical Observation	**Clear solution**	**Clear solution No change**	**Clear solution No change**	**Clear solution No change**
Assay for Propofol content	**100.3%**	**84.6%**	**93.7% ***	**65.0%**	Assay for Propofol content	**99.06%**	**99.98%**	**99.93%**	**98.89%**

* This result is expected because of non homogenecity of the solution.

The above results clearly indicate the superiority of the present ready to use clear solution over the Emulsion formulation containing Ketamine when prepared using the above ratio of 100 : 5 The premixed emulsion formulation shows a phase separation and there is a pain elicitated by irritation, oedema and erythema. No such phenomena is observed in the clear composition of the invention. The solution remains physically stable without loss of potency.

Example 9

A solution containing mixture of Ketamine in emulsion formulation in the ratio according to Ho-yeung Kil et.al., is prepared by conventional method of premixing. The readily available two 10 ml portion of emulsion containing 10 mg/ml of Propofol of is taken in two clean and sterilized separate Vials and mixed with 16.66 mg and 33.22 mg of Ketamine respectively and thoroughly mixed to ensure solubility According to the prior art, the solution in emulsion contains Propofol : Ketamine in the ratio of 100 : 16.66 and 100 : 33.32 This is compared with the composition of the present invention containing Propofol : Ketamine in the ratio of 100 : 5 prepared as previously cited . The stability studies were carried out for the Assay of Propofol content of the premixed solution as well as composition of the present invention at the interval of 1 hr, 3 hrs & 24 hrs as mentioned in the prior art.

The results are illustrated in table below:

Propofol : Ketamine 100 : 5				Propofol : Ketamine 100 : 16.66				Propofol : Ketamine 100 : 33.32			
	1 hr	**3 hrs**	**24 hrs.**		**1 hr**	**3 hrs**	**24 hrs**		**1 hr.**	**3 hrs.**	**24 hrs.**
Description, Physical Observation	Clear Solution Homoge -neous	Clear solution Homoge - neous	Clear solution Homoge - neous	**Description, Physical Observation**	Separation of the phases. Oily globules floating Non Homoge - neous	Separation of the phases. Oily globules floating Non Homoge -neous	Separation of the phases. Oily globules floating Non Homoge - neous	**Description, Physical observation**	Separation of the phases. Oily globules floating Non Homogen-eous	Separation of the phases. Oily globules floating Non homogene -ous	Separation of the phases. Oily globules floating Non Homogen eous
Identification of Ketamine	Complies	Complies	Complies	**Identification of Ketamine**	Complies	Complies	Complies	**Identification, of Ketamine**	Complies	Complies	Complies
Assay for Propofol content	99.96%	99.98%	99.93%	**Assay for Propofol content**	100.3%	90.87% *	97.45%	**Assay for Propofol content**	100.5%	84.6% *	93.7%

* Since solution is non-homogeneous the results of the drug percentage may vary.

It is observed that the composition of the present invention with Propofol : Ketamine in the ratio of 100:5 gives a homogenous clear solution with no phase separation . Moreover the concentration of Propofol is maintained. On the other hand the solution in emulsion containing Propofol : Ketamine in the ratio of 100 : 16.66 and 100 : 33.32 according to the prior art there occurs phase separation with oily globules floating. The concentration of the Propofol however is maintained in these concentration too.

Further stability of the injections were tested for Propofol content by stability indicating HPLC method. The results are indicated above.

Efficacy studies :

The Efficacy study has not been pursued because of the separation of the phases in the emulsion. As the phase separation is there even at the ratio of 100 : 5 in the emulsion formulation, 100 : 1 mg of Ketamine in the emulsion was prepared and still there was a phase separation and colouration of the solution. This can be attributed to incompatibility of Ketamine in the emulsion. No such phenomena occurred in the clear solution of the invention.

CLAIMS

1. A ready to use stable anaesthetic composition in the form of a clear solution comprising (i) Propofol; (ii) at least one analgesic and like drug and (iii) antioxidants, all being in a solvent system selected from (a) water and 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and/or its derivatives (b)cyclodextrin and its derivative and water, wherein cyclodextrin forms a complex with Propofol.

2. A composition according to claim 1 wherein the solvent system is water and 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and/or its derivative.

3. A composition according to in any one of claims1 and 2 wherein 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and water is in the range from 70 to 30: 30 to 70, preferably in the ratio of 65: 35.

4. A composition according to any one of claims 1 to 3 wherein Propofol concentration is in the range of from 1% to 3% w/v, preferably 1% w/v.

5. A composition according to in any one of claims 1 to 4 wherein the analgesic is selected from Lignocaine, Ketamine, Tramodol, Alfentanil, Pethidine, Ropivacaine, Bupivacaine, Ketamine and the like capable of being administered parenterally.

6. A composition according to in any one of claims 1 to 5 wherein Propofol and Ligocaine present in the wt/wt ratio of 10 :1 to 300:1, preferably 100:1

7. A composition according to in any one of claims 1 to 5 wherein Propofol and Ketamine present in the wt/wt ratio of 10:5 to 300: 5, preferably 100:5

8. A composition according to in any one of claims 1 to 6 wherein concentration of Lignocaine in the range from 0.001 to 0.1% preferably 0.01%.

9. A composition according to in any one of claims 1 to 5 and 7 wherein concentration of that of Ketamine in the range of 0.001 to 0.1% preferably 0.05%.

10. A composition according to in any one of claims 1 to 5 wherein concentration of Tramadol in the range from 0.01% to 0.05%.

11. A composition according to in any one of claims 1 to 5 wherein concentration Fentanyl is in the range of 0.001% to 0.0015%.

12. A composition according to in any one of claims 1 to 5 wherein concentration of Alfentanil is in the range of 0.001% to 0.005%.

13. A composition according to in any one of claims 1 to 5 wherein concentration of Pethidine is in the range of 0.010% to 0.05% preferably 0.04%.

14. A composition according to any one of claims 1 to 13 wherein the antioxidant is selected from the group of Vitamin E derivatives, Ascorbates, preferably Alpha Tocopherol

15. A composition according to any one of claims 1 to 14 wherein the concentration of said antioxidant is in the range of 0.01% to 0.2% and preferably 0.1% w/v.

16. A composition according to any one of claims 1 to 15 wherein the pH is between 5.0 to 7.0, preferably 6.4

17. A composition according to claim 1 wherein the solvent system is matrix of cyclodextrin and its derivatives and water, wherein Propofol being complexed with cyclodextrin.

18. A composition according to claim 1 and 17 wherein cyclodextrin and Propofol is in the ratio of 1:3, preferably 1:1.

19. A process for preparation of ready to use stable anaesthetic composition in the form of a clear solution comprising (i) propofol, (ii) at least one analgesic and like drug (iii) antioxidants, all being in a solvent system selected from (a) water and 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and/or its derivatives (b) cyclodextrin and its derivative and water wherein cyclodextrin forms a complex with Propofol comprising the steps of:

    a. mixing Propofol in solvent system for effective dissolution of Propofol followed by addition of analgesic agents and further addition of antioxidants in the desired quantity and mixing;
    b. adjusting the pH
    c. filtering the mixture
    d. filling in multidose vials

20. A process according to claim 19 wherein the solvent system used is water and 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and/or its derivatives.

21. A process according to any one of claims 19 and 20 wherein Propofol used is in concentration in the range of from 1% to 3% w/v, preferably 1% w/v.

22. A process according to in any one of claims19 to 21 wherein 2,5 di-omethyl-1,4;3,6-dianhydro-D-glucitol and water mixture used is in the range from 70 to 30: 30 to 70, preferably in the ratio of 65: 35.

23. A process according to in any one of claims 19 to 22 wherein the analgesic used is selected from Lignocaine, Ketamine, Tramodol, Alfentanil, Pethidine, Ropivacaine, Bupivacaine and other drugs like Ketamine capable of being administered parenterally.

24. A process according to in any one of claims 19 to 23 wherein Propofol and Ligocaine present in the wt/wt ratio of 10: 1 to 300:1, preferably 100:1

25. A process according to in any one of claims 19 to 23 wherein Propofol and Ketamine present in the wt/wt ratio of 10:5 to 300:5, preferably 100:5

26. A process according to in any one of claims 19 to 24 wherein concentration of Lignocaine in the range from 0.001 to 0.1% preferably 0.01%.

27. A process according to in any one of claims 19 to 23 and 25 wherein concentration of that of Ketamine in the range of 0.001 to 0.10% preferably 0.05%.

28. A process according to in any one of claims 19 to 23 wherein concentration of Tramadol in the range from 0.01% to 0.05%.

29. A process according to in any one of claims 19 to 23 wherein concentration Fentanyl is in the range of 0.001% to 0.0015%.

30. A process according to in any one of claims 19 to 23 wherein concentration of Alfentanil is in the range of 0.001% to 0.005%.

31. A process according to in any one of claims 19 to 23 wherein concentration of Pethidine is in the range of 0.010% to 0.05% preferably 0.04%.

32. A process according to any one of claims 19 to 31 wherein the Antioxidant is selected from the group of Vitamin E derivatives, Ascorbates, preferably Alpha Tocopherol

33. A process according to any one of claims 19 to32 wherein pH is maintained at 5 to 7, preferably 6.4 with acid or alkali.

34. A process according to any one of claims 19 to 33 wherein filtering is done through 0.22 μ Nylon filter under aseptic condition.

35. A process as claimed in any one of claims 19 to 34 wherein filling in multidose vials is followed by sealing and sterilization for ready to use.

36. A process according to claim 19 wherein solvent matrix system used is cyclodextrin and its derivative and water wherein cyclodextrin forms a complex with Propofol.

37. A process according to claim 36 wherein cyclodextrin is mixed with propofol in a ratio of 1:3, preferably 1:1 to form a complex, said complex is dissolved in water and analgesics and antoxidants are then added and mixed.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN03/00217

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 9/08, 31/05, 31/34 A61P 23/00, 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPIDS, CHEMICAL ABSTRACTS, MEDLINE and keywords: propofol,diprivan,2,6-diisopropylphenol, disoprivan, rapinovet,lignocaine,lidocaine, ketamine, tramadol,alfentanil,pethidine,ropivacaine,bupivacain

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/074200 A (CYDEX INC.) 26 September 2002 Page 32 lines 18-24, page 37 example 5.	1,4-8,19,21,23-37
X	US 6071974 A (PATEL et al) 6 June 2000 Abstract, column 3 line 41.	1-8,19-37
X	US 6071933 A (Joo et al) 6 June 2000 Example 1 column 4 line 65 to column 5 line 7.	1-8,19-37

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2003	19 DEC 2003
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **ANDREW ACHILLEOS** Telephone No : (02) 6283 2280

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN03/00217

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5962536 A (KOMER) 5 October 1999 Column 1 line 65 to column 2 line 7, column 2 lines 45-46, Examples 3 and 4.	1-8,19-37
X	US 4056637 A (GLEN JB) 1 November 1977 Column 6 example 11 and column 7 example 12.	1-8,19-37
A	Medline Abstract 1731545 King et al, "Lidocaine for the prevention of pain due to injection of propofol", *Anesth.Analg.*, Vol 74(2), 1992, p 246-9. Abstract	1-8,19-37
A	Medline Abstract 2646847 Valtonen et al, "Propofol as an induction agent in children: pain on injection and pharmacokinetics", *Acta Anaesthesiol Scand.*, Vol 33(2), 1989, p 152-5. Abstract	1-8,19-37

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN03/00217

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	02074200	US	2003055023	US	2003073665	WO	03080079
US	6071974	AU	18887/00	EP	1143962	WO	0044369
US	6071933						
US	5962536	AU	51368/99	CA	2338684	EP	1131062
		NZ	510469	WO	0006142		
US	4056637						

END OF ANNEX