“柏朗”普洛福 靜脈注射液
Propofol-Lipuro 1%

1. 藥品名稱
Propofol-Lipuro 10 mg/ ml

2. 主成分
本藥品內含

	每1 ml	每20 ml之安瓿	每50 ml之小瓶	每100 ml之小瓶
Propofol	10 mg	200 mg	500 mg	1000 mg

具有已知效果的賦形劑：
1 ml用於注射或輸注之乳劑含有
Soya-bean oil, refined 50 mg
Sodium 0.03 mg
賦形劑之完整列表，請參考第6.1節。

3. 劑型：
注射或輸注之乳劑
乳白色水包油乳劑

4. 臨床詳細資料

4.1 適應症
本藥品為短效之靜脈全身麻醉劑，適用於：
- 成人及1個月以上幼童之全身麻醉誘導或維持
- 加護病房中使用人工呼吸器之超過16歲成人病人之鎮靜
- 成人病人診斷及外科手術過程中鎮靜之用，可單獨使用或與其他局部麻醉劑或全身麻醉劑合併使用

4.2 用法用量及給藥方式
一般說明
本藥品必須由受過麻醉劑訓練或照顧加護病房之病人的醫師，在醫院或設備充足的日常治療機構中進行注射。必須持續監控循環及呼吸功能，例如：心電圖(ECG)、脈衝式血氧儀(pulse-oxymeter)以及維持病人呼吸道暢通、人工換氣及其他復甦設備必須隨時準備妥當。針對利用本藥品於手術或診斷程序中進行鎮靜的情況，不可由進行手術或診斷程序之醫師進行。
本藥品禁止用於加護病房中16歲以下的病人之鎮靜(請參考第4.3節)。該族群的安全性和有效性尚未得到證實。
除了本藥品之外，一般還需要準備止痛藥品。
用法和用量
本藥品藉由靜脈注射，且必須依照病人的反應個別調整劑量。
- 成人之全身麻醉
  全身麻醉之誘導
  本藥品可用於麻醉誘導(每10秒給予20-40 mg)，建議應該依照病人的反應來調整劑量，一直到麻醉作用已開始的臨床現象出現為止。大部分55歲以下的成年人，每公斤體重大約需要1.5-2.5 mg。55歲以上及美國麻醉醫學會(ASA)分類第3級和第4級的病人，尤其是心臟功能受損者，對於本藥品之需求劑量較低且其總給藥量可能降至最低劑量每公斤體重1 mg。對於這些病人給藥速度應減慢(約2 ml，相當於20 mg/10 sec.)。
  全身麻醉之維持
  麻醉可藉由持續輸注或重覆短期注射(bolus injections)本藥品來維持。若使用重覆短期注射之技術，可依臨床需求增量給予25-50 mg(即本藥品2.5-5.0 ml)。若以持續性靜脈點滴輸注做為全身麻醉維持，需求之劑量通常為介於4-12 mg/kg body weight/h。
  在老年病人、一般狀況較差的病人、美國麻醉醫學會分類第3級和第4級病人與低血容積(hypovolaemic)病人，應依照病人病情的嚴重程度和麻醉方式進一步地減輕劑量。
- 年齡1個月以上兒童之全身麻醉
  全身麻醉之誘導
  針對麻醉誘導，本藥應慢慢地根據病人反應滴定給予，直到臨床表徵顯示麻醉作用開始奏效。劑量應視年齡及/或體重而調整。
  大多數超過8歲的病人，需要大約2.5 mg/ kg body weight的本藥品作為麻醉誘導。而較小的兒童，尤其是年齡在1個月到3歲之間的兒童，需求劑量可能要高一些(2.5-4 mg/kg body weight)。
  全身麻醉之維持
  麻醉可藉由持續輸注本藥品來維持所需要的麻醉深度。給藥速度在不同病人間有較大差異，但一般而言給予9-15 mg/kg/h的速度範圍，可以達到理想的麻醉效果。在較小的兒童，尤其是年齡在1個月到3歲之間的兒童，劑量需求可能會較高一些。針對美國麻醉醫學會分類第3級和第4級的病人，建議給予較低劑量(請同時參閱第4.4節)。
- 加護病房中使用人工呼吸器病人之鎮靜
  加護病房內使用人工呼吸器病人進行鎮靜時，建議以持續輸注方式給藥。輸注速率應以所需之鎮靜深度而定。對多數病人而言，介於0.3-4 mg/kg body weight/h之劑量速率，即可維持足夠的鎮靜效果。(請同時參閱第4.4節)。本藥品不可用於加護病房中年齡為16歲以下病人之鎮靜(請參閱第4.3節)。
  不建議在加護病房以標靶控制輸注(Target Controlled Infusion，TCI)系統給予本藥品作鎮靜之用。
- 成人診斷及外科手術過程中之鎮靜
  於外科手術及診斷過程提供鎮靜，其劑量與給藥速率應視臨床反應而定；大多數病人需要0.5-1 mg/kg body weight，給予1至5分鐘時鎮靜作用開始奏效。維持鎮靜作用，可以藉由調整本藥的滴定輸注至所需之鎮定程度來達成；多數病人需要1.5-4.5 mg/kg body weight/h的投藥速率。若需快速增加鎮靜深度，可利用短期注射靜脈投予10-20 mg 本藥品(即本藥1-2 ml)。
  針對年齡超過55歲之病人及美國麻醉醫學會分類第3級和第4級的病人，可能需要較低劑量且其投藥速率也可能需要降低。
- 本藥品不建議使用於年齡小於16歲的兒童之診斷及外科手術過程中之鎮靜。

投藥方式與期間
- 投藥方式
  靜脈給藥
  本藥品可透過靜脈注射或持續性點滴輸注方式給予，可不經稀釋直接給藥或利用5% w/v glucose輸注液、0.9% w/v sodium chloride輸注液稀釋後使用(請同時參閱第6.6節)。
  使用前必須混搖均勻。
  使用前，安瓿的瓶頸或小瓶的橡膠塞子表面必須以藥用酒精(噴霧或棉片)進行清潔。使用後，覆面容器必須丟棄。
  本藥品不含抗微生物防腐劑並能支持微生物生長。因此，在打開安瓿或小瓶的密封後，應立即將本藥品無菌地抽入無菌注射器或輸注設備。輸注必須立刻開始。在整個輸注期間必須保持本藥品及輸注設備的無菌狀態。
  任何藥品或液體添加到正在輸注的Propofol輸液，必須靠近套管部位。如果使用帶有微生物過濾器的輸注設備，這些必須是能通過脂質的。一個安瓿或一個小瓶的Propofol，以及含有Propofol的注射器都是單人單次使用。
  本藥品未經稀釋輸注
  當本藥品未經稀釋持續輸注時，建議持續使用流速滴定管(burettes)、液滴計數器(drop counters)、注射幫浦(syringe pumps)或體積測定輸注幫浦(volumetric infusion pumps)以控制輸注速率。輸注結束或更換輸液系統後，殘餘之藥品應丟棄。如同針對所有種類脂肪乳劑之靜脈輸注所建立的規定，經由同一輸液系統輸注本藥品的時間不宜超過12小時。本藥品之輸液管及儲藥器，至多使用12小時後即須丟棄並更換。
  本藥品稀釋輸注
  當本藥品稀釋後持續輸注時，建議持續使用流速滴定管、液滴計數器、注射幫浦或體積測定輸注幫浦以控制輸注速率，且避免不慎失控注射大量稀釋藥品之風險。
  利用5% w/v glucose輸注液、0.9% w/v sodium chloride輸注液稀釋本藥品時，其最大稀釋量為1:4，(稀釋液之濃度不可低於2 mg Propofol/ml)。且應於投藥前即時以無菌操作調配，並務必於調配完成後 6小時內使用。為降低注射部位在輸注初期之疼痛感，本藥品可與不含防腐劑之 Lidocaine 1%注射劑調配(亦即，本藥品20份，至多與1份之Lidocaine 1% 注射劑調配)。若在注射本藥品後，隨之以同一輸液管路投予肌肉鬆弛劑 atracurium 或 mivacurium ，應於投藥前將注射管路沖淨。本藥品不得與第6.6節中未提到的藥品混合。
- 投藥期間
  本藥品之投藥期間至多為七天。

4.3 禁忌
- **禁止用於已知對本藥品主成分或第6.1節所列任何賦形劑過敏的病人。**
- **本藥含有大豆油，不可用於大豆、花生過敏之病人。**
- **本藥品不可用作年齡在16歲以下加護病房病人之鎮靜劑。(請參閱第4.4節)**

4.4 特殊警語與使用注意事項
- **本藥品須由接受過麻醉相關訓練的人員(或若情況適當時，由接受過照顧加護病房病人訓練之醫師進行)給藥。**
- **須持續監控病人，維持呼吸道暢通、人工換氣、氧氣供應及其他復甦設備必須隨時準備妥當。本藥品不可由執行診斷及外科手術的人員給藥。**
- **主要由醫護人員造成之本藥品濫用和依賴的情形已有相關報告。如同其他全身麻醉劑，使用本藥品時，若未維持呼吸道暢通可能導致致命的呼吸系統併發症。**
- **當本藥品用於手術及診斷之有意識鎮靜時，應持續監控病人，以期及早發現是否有低血壓、呼吸道阻塞和血氧未飽和的症狀發生。**
- **如同其他鎮靜劑，當本藥品於手術進行中用於鎮靜時，病人可能出現非自主性抽動。當進行需要完全不動、放鬆肌肉的手術時，非自主抽動可能會對手術部位造成傷害。**
- **病人出院前需要停留一段足夠的恢復時間以確保病人已完全脫離本藥品的影響。使用本藥品的病人可能有極少數會在術後產生意識不清的情況，也可能伴隨肌肉緊張的情況。此類情況可能發生於清醒之後。雖然恢復是自發的，但仍須給予意識不清病人適當的照護。**
- **本藥品導致的功能不良一般來說並不會在用藥後12小時以後被察覺。針對下列情況在提供病人建議時，本藥品的效用、手術、併用藥品、年齡和病人的狀況均應予以考慮：**
  - **是否需要陪伴才能離開投藥地點**
  - **可以再次從事技術性或具危險性工作的時間；如，駕駛車輛**
  - **使用其他具有鎮靜功用的藥品(例如：苯二氮泮類安眠鎮靜劑(benzodiazepines)、鴉片製劑(opiates)和酒精)**
- **如同其他靜脈麻醉劑，必須特別留意心臟、呼吸、腎臟或肝臟功能損傷之病人以及低血容或體弱病人。(請同時參閱4.2節)**
- **本藥品的清除依靠血流。因此，會降低心輸出量的併用藥品將導致本藥品的清除率下降。**
- **電痙攣治療時不建議使用本藥品。**
- **對於嚴重心臟功能損傷之病人，使用本藥品必須非常謹慎同時持續嚴密監測。**
- **本藥品缺乏抑制迷走神經傳導活性(vagolytic activity)，可能會引起心搏過緩(bradycardia)(偶有嚴重案例)及心搏停止(asystole)。在麻醉誘導前或麻醉維持期間應考慮靜脈注射抗膽鹼劑(anti-cholinergic agent)，特別是在迷走神經衝動(vagal tone)可能較佔優勢之情況下，或本藥品與可能會引起心搏過緩之藥品併用時。**
- **癲癇病人投予本藥品可能有引發痙攣之風險。在癲癇病人麻醉之前，應檢查病人是否接受癲癇治療。**
- **對於脂肪代謝障礙或須限制脂肪乳劑使用之病人，必須特別謹慎。**
- **兒童族群**
  本藥品不建議用於年齡小於一個月的新生兒，因該病人群體尚未完全研究。藥物動力學數據(請參閱第5.2節)顯示新生兒的清除率顯著降低，且具有非常高的個體間變異性。兒童建議劑量有可能引起相對地過量，導致嚴重心血管抑制。本藥品不能用於加護病房中16歲以下的病人之鎮靜，因為該族群中將本藥品用於鎮靜的安全性和有效性尚未確立。雖然目前尚未有因果關係之建立，非適應症使用於年齡小於16歲兒童鎮靜的嚴重不良反應事件(包含有致命結果的案例)已有相關通報，特別是這些副作用與代謝性酸中毒、高血脂症、橫紋肌溶解及/或心臟衰竭的發生有關。上述副作用常見於加護病房中使用劑量高於成人劑量之呼吸道感染的幼童。(請參閱第4.3節)
- **加護病房中使用之建議**
  本藥品於加護病房中做為鎮靜之用，已經證實與可能導致死亡的代謝紊亂及系統器官衰竭相關。
  相關通報包含下列不良反應：代謝性酸中毒、橫紋肌溶解症、高血鉀症、肝腫大、腎臟衰竭、高血脂症、心律不整、布魯格達氏(Brugada-type)心電圖(ST段上升和拱型T波) 以及對強心支持性治療無良好反應之快速惡化的心臟衰竭。結合上述症狀被歸納為Propofol輸注症候群(Propofol infusion syndrome)。
  下列情況可視為發生上述事件最主要的危險因子：組織氧氣量減少、嚴重神經損傷及/或敗血症，以及以高劑量使用下列的一種或多種藥品：血管收縮劑、類固醇、強心劑和/或本藥品(通常使用大於4 mg/kg/h的給藥速率持續超過48小時)。
  處方者必須注意上述事件，並在上述跡象發生時及時考慮減少或停止本藥品的劑量。所有使用於加護病房內的鎮靜劑及治療藥品，包括本藥品，必須以適定的方式注射，以維持最佳氧氣輸送和血流動力學參數。合併有顱內壓上升的病人，在改變治療方式時，必須給予適當之治療，以維持大腦灌流。施行治療的醫師必須記得若情況許可，劑量不可超過4 mg/kg/h。
  適當的護理應該應用於脂肪代謝紊亂的病人，以及必須謹慎使用脂肪乳劑的狀況下。病人若有脂肪負荷過重(fat overload)的特殊風險，建議在注射本藥品時監控血脂狀況。若監控顯示脂肪自體內清除異常，則必須適當調整本藥品的投予。如果病人同時接受其他靜脈脂肪營養，則必須減少脂肪輸注量並將本藥品所含之脂肪納入考量：本藥品1.0 ml含有0.1 g之脂肪。在加護病房使用超過三天，應監測其脂肪。
- **其他注意事項**
  治療粒線體遺傳疾病人時應謹慎。這些病人在接受麻醉、手術和及在加護病房中照護時可能使其病症惡化。建議為這些病人維持正常體溫，提供碳水化合物及良好的輸液。粒線體遺傳疾病惡化和Propofol輸注症候群的早期表徵可能是類似的。
  本藥品不含抗菌防腐劑且可能滋生微生物。
  當要抽出本藥品時，必須在打開安瓿或破壞小瓶之密封後，在無菌操作下，立刻抽入無菌針筒或輸液裝置。輸注程序必須立刻開始。輸注期間，本藥品和輸液設備必須保持無菌。本藥品正在輸注時，加入任何藥品或輸液，必須在靠近管路旁叉部位執行。本藥品以及任何裝有本藥品之針筒皆為單次/單一病人使用。根據其他脂肪乳劑已建立的規範，經由同一輸液系統之本藥品輸注時間不宜超過12小時。輸注完成或12小時之後，以較早者為準，輸注管路及剩餘之本藥品應予以丟棄並適當更換。
- **關於賦形劑的特殊警告與注意事項**
  本藥品100 ml之鈉含量少於1 mmol (23 mg)，意即基本上是「不含鈉」。

4.5 與其他藥品及其他劑型之交互作用
本藥品用於脊椎及硬脊膜之麻醉，和常用的術前用藥、神經肌肉阻斷劑、吸入性麻醉劑及止痛劑併用；目前並無藥理作用不相容的情況發生。施行區域麻醉時，若需併用全身麻醉或鎮靜作為輔助，可使用較低劑量的本藥品。
同時施打其他中樞神經抑制劑，如術前用藥、吸入劑、止痛劑，會增強本藥品的鎮靜、麻醉和心肺抑制作用。

4.6 妊娠與授乳
- **妊娠**
  懷孕期使用本藥品的安全性目前尚未得知。除非絕對必要，否則不可將本藥品用於懷孕的婦女。本藥品會透過胎盤並造成新生兒抑制。然而，本藥品可以使用於人工流產。
- **授乳**
  研究顯示少量的本藥品會藉由乳汁分泌。因此在注射本藥品後，24小時內不可哺乳，上述期間內所分泌的乳汁應予以丟棄。
- **生育**
  尚無資料。

4.7 對開車及操作機械能力的影響
需告知病人進行技術性工作(例如：開車及操作機械)的表現可能在使用本藥品後的一段時間內會受到影響。本藥品導致的功能不良一般來說並不會在用藥後12 小時以後被察覺(請參閱第4.4節)。

4.8 不良反應
本藥品用於麻醉的誘導與維持或是鎮靜效果通常是平穩的，且具有極少證據的刺激性。最常報告的不良反應為麻醉或鎮靜劑在藥理學上可預見之反應，例如低血壓。這些反應取決於所用的藥品劑量，也取決於預處理和其他併用藥品的類型。接受本藥品病人的不良反應之性質、嚴重程度和發生率可能與病人狀況及手術或診斷的種類有關。
不良反應表
不良反應根據其頻率列出如下：
非常常見 (≥1/10)
常見 (≥1/100 至 < 1/10)
不常見 (≥1/1,000 至 < 1/100)
少見 (≥1/10,000 至 < 1/1,000)
非常罕見 (<1/10,000)
頻率未知（無法從可取得之數據中估算出頻率）

器官系統分類	頻率	不良反應
免疫系統異常	非常罕見	過敏性休克前的過敏反應：可能包括血管性水腫、支氣管痙攣、紅斑和低血壓
新陳代謝和營養失調	頻率未知[9]	代謝性酸中毒[5]、高血鉀症[5]、高血脂症[5]
精神異常	頻率未知[9]	欣快感(euphoric mood)、濫用和依賴[8]
神經系統異常	常見	恢復期頭痛
	少見	在誘導、維持和恢復期發生癲癇型動作(epileptiform movement)，包括抽搐和角弓反張(opisthotonus)。
	非常罕見	術後意識不清
	頻率未知[9]	不自主抽動
心臟異常	常見	心搏過緩[1]
	非常罕見	肺水腫
	頻率未知[9]	心律不整[5] 、心臟衰竭[5] [7]
血管異常	常見	低血壓 [2]
呼吸、胸腔和縱膈異常	常見	誘導期間暫時性呼吸中止
	頻率未知[9]	呼吸抑制(與劑量相關)
腸胃異常	常見	恢復時期噁心或嘔吐
	非常罕見	胰臟炎
肝膽異常	頻率未知[9]	肝腫大[5]
肌肉骨骼和結締組織異常	頻率未知[9]	橫紋肌溶解症(rhabdomyolysis)[3][5]
腎臟和泌尿系統異常	非常罕見	長時間注射後出現尿液變色
	頻率未知[9]	腎衰竭 [5]
生殖系統和乳房異常	非常罕見	性抑制解除(sexual disinhibition)
一般性的異常和投藥部位狀況	非常常見	誘導期發生局部疼痛 [4]
	不常見	注射部位血栓及靜脈炎
	非常罕見	不慎血管外給藥後的組織壞死[10] [11]
	頻率未知[9]	不慎血管外給藥後局部疼痛、腫脹和發炎[11]
檢查數值	頻率未知[9]	布魯格達氏心電圖 [5] [6]
受傷、中毒和手術併發症	非常罕見	術後發燒

(1) **罕見嚴重心搏過緩。有獨立個案惡化為心搏停止。**
(2) **偶爾會發生低血壓需要使用靜脈液體及減少本藥品注射速率的情況。**
(3) **關於本藥品大於4 mg/kg/hr之劑量在加護病房內用於鎮靜的情況，有非常少的報告結果產生橫紋肌溶解症。**
(4) **可以藉由選擇前臂及肘前窩處較大靜脈血管進行注射來減低疼痛。同時可以併用Lidocaine來減低局部疼痛。**
(5) **這些反應併稱為「Propofol輸注症候群」，可能在罹患嚴重疾病並有多個可能引發這些反應之危險因子的病人身上發生。(請參閱第4.4節)**
(6) **布魯格達氏心電圖ST段上升和心電圖上的拱型T波。**
(7) **成人的快速惡化的心臟衰竭（部分案例中產生致命結果）。前述案例中，心臟衰竭通常對強心支持性治療無良好反應。**
(8) **主要由醫護人員造成之藥品濫用與依賴情形。**
(9) **由於無法藉由已取得之臨床實驗數據加以評估，所以目前尚未得知。**
(10) **組織存活性受損的壞死案例已被報導。**
(11) **症狀治療，可能包括固定及(如果可以的話)抬高受影響的肢體、冷卻、密切觀察，必要時照會外科醫師。**

4.9 過量
症狀
意外的藥劑過量可能會造成心肺功能抑制。
治療
呼吸抑制時，應利用人工換氣來更換氧氣進行治療。心血管抑制可能需要降低病人頭部位置，若情況嚴重，請使用血漿擴張劑及升壓劑。

5. 藥理學特性

5.1 藥效特性
- 藥理分類：其他全身麻醉劑，ATC code：N01AX10
- 作用機制、藥效作用
  靜脈注射Propofol後，催眠作用快速產生。依據輸注速率，麻醉誘導期間為30至40 秒間。因為快速地代謝與排除，所以單次短期注射作用持續的時間短暫(4-6 分鐘)。
  依照建議劑量，在重覆短期注射或在持續輸注後，臨床上並未發現Propofol有顯著的累積。
  病人會快速地恢復意識。心搏過緩與低血壓偶爾會在麻醉過程中發生，可能是因為缺乏抑制迷走神經傳導活性之故。心肺循環狀態通常在麻醉維持期恢復正常。
  與純的長鏈三酸甘油脂乳劑相比，混合中、長鏈三酸甘油脂乳劑的Propofol製劑在水相中游離藥物的濃度較低。該現象可以解釋：在比較性臨床研究中所觀察到之Propofol乳劑所減少的疼痛頻率與強度，是由於非常低的游離Propofol濃度所致。
  兒科族群
  關於Propofol作為麻醉劑使用於兒童身上之麻醉時間的研究有限，然顯示出安全性和有效性至4 小時仍不變。使用於兒童的文獻證明，延長使用時間對於安全性與有效性不會有所改變。

5.2 藥物動力特性
- 分佈
  在靜脈投藥後約98%之Propofol會與血漿蛋白結合。
  靜脈短期注射後，Propofol的初始血液濃度由於快速分佈到不同的腔室(α相)中而迅速下降。分佈半衰期經計算為2-4 分鐘。
  排除過程中血液濃度的下降速度較慢。其在β相中的代謝半衰期為30-60分鐘。隨後，第三深腔室(third deep compartment)變得明顯，顯示來自弱灌注組織(weakly perfused tissue)的Propofol重新分佈。
  中央分佈體積為0.2-0.79 L/kg body weight，穩定期分佈體積為1.8-5.3 L/kg body weight。
- 生物轉化
  Propofol的代謝主要在肝臟，形成Propofol葡萄糖醛酸(glucuronides)、葡萄糖醛酸與其相應對苯二酚(quinol)之硫酸鹽複合物(sulphate conjugates)。所有的代謝物皆沒有活性。
- 排除
  Propofol從身體中快速地被清除(完全清除所需時間約2 L/min)。清除主要在肝臟中，由代謝現象產生，並取決於血流量。兒童與成人相較之下，前者清除率較快。投藥劑量中約88%會藉由尿液以代謝物的形式排出，只有0.3%以原型由尿液排泄。
- 兒科族群
  靜脈注射單次3 mg/kg劑量後，Propofol每公斤體重的清除率隨著年齡增加：與較年長的兒童(n=36，年齡範圍4個月至7歲)相較，小於1個月的新生兒(n=25)的平均清除率較低(20 m/kg/min)。
  此外，個體間差異在新生兒身上比較明顯(範圍介於3.7-78 ml/kg/min)。因為有限的研究數據顯示極大的差異性，所以無法針對這個年齡族群提供建議劑量。
  靜脈注射單次3 mg/kg劑量後，較年長兒童的Propofol平均清除率為37.5 ml/min/kg (n=8) (4-24個月)，38.7 ml/min/kg (11-43個月)（n=6），48 ml/min/kg（1-3歲）（n=12），28.2 ml/min/kg（4-7歲）（n=10）；成人則為23.6 ml/min/kg（n=6）。

5.3 臨床前安全性數據
臨床前數據顯示，傳統之重覆劑量毒性和遺傳毒性試驗無觀察到特定對人類有害之毒性。致癌性研究目前尚未進行。
生殖毒性研究已顯示，在高劑量下會產生與藥效學特性有關的影響，增加胚胎著床後失敗率及減少子代存活率。致畸胎作用目前尚未觀察到。在局部耐受性研究中，肌肉注射可能導致注射部位周圍組織損傷。

6. 藥品特點

6.1 賦形劑列表
Soya-bean oil, refined，medium-chain triglycerides，glycerol，egg lecithin， sodium oleate，water for injection

6.2 不相容性
除了第6.6節中所述的產品外，本藥品不可與其他產品混合調配使用。

6.3 保存期間
2年。
有效期限：本藥品須在標籤上之有效期限前使用。
第一次打開後：
請馬上使用
依照指示稀釋後：
稀釋調配完成後需立即進行注射

6.4 儲存特殊警語
儲存溫度不可超過 25 °C。
不可冷凍。

6.5 容器材質及內容物
無色的第I型玻璃安瓿內含有20 ml的乳化劑。
無色的第II型玻璃小瓶，以bromobutyl橡膠塞及鋁蓋密封，內含有50ml或100 ml的乳劑。
包裝尺寸：
玻璃安瓿：5 x 20 ml
玻璃小瓶：1 x 50 ml，10 x 50 ml，1 x 100 ml，10 x 100 ml
並非所有包裝尺寸皆上市。

6.6 丟棄與調配特殊警語
任何未使用的產品或廢棄材料應依照當地法規丟棄。
使用前必須搖晃均勻。
僅供單次使用。使用後任何剩餘的內容物都必須丟棄，請參閱第4.2節。
若搖晃藥品後目視呈現二層，則應丟棄不可使用。
本藥品只可以和下列藥品混合調配：50 mg/ml (5% w/v) glucose輸注液、9 mg/ml (0.9% w/v) sodium chloride輸注液和不含防腐劑的 Lidocaine 10 mg/ml (1%)（請參閱第4.2節）。
可經由Y 型管 (Y-connector) 在接近注射部位輸注本藥品與50 mg/ml (5% w/v) glucose 輸注液、9 mg/ml (0.9% w/v) sodium chloride 輸注液。

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B. Braun Melsungen AG
34209 Melsungen, Germany

B. Braun Melsungen AG · 34209 Melsungen · Germany

Propofol-Lipuro 1% (10 mg/ml)

1. NAME OF THE MEDICINAL PRODUCT

Propofol-Lipuro 10 mg/ml emulsion for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Propofol-Lipuro 10 mg/ml contains

	per 1 ml	per 10 ml ampoule	per 20 ml ampoule or vial	per 50 ml vial	per 100 ml vial
Propofol	10 mg	100 mg	200 mg	500 mg	1000 mg

Excipients with known effect:
1 ml of emulsion for injection or infusion contains
Soya-bean oil, refined 50 mg
Sodium 0.03 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for injection or infusion
White milky oil-in-water emulsion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Propofol-Lipuro 10 mg/ml is a short-acting intravenous general anaesthetic indicated for
- induction and maintenance of general anaesthesia in adults and children > 1 month
- sedation of ventilated patients >16 years of age in the intensive care unit
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults.

4.2 Posology and method of administration

General instructions

Propofol-Lipuro 10 mg/ml should be given in hospitals or adequately equipped day therapy units by physicians trained in anaesthesia or in the care of patients in intensive care. Circulatory and respiratory functions should be constantly monitored (e.g. ECG, pulse-oxymeter) and facilities for maintenance of patent airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times. For sedation during surgical or diagnostic procedures Propofol-Lipuro 10 mg/ml should not be given by the same person that carries out the surgical or diagnostic procedure.
Propofol is contraindicated in patients of 16 years of age or younger for sedation for intensive care (see section 4.3). Safety and efficacy for these age groups have not been demonstrated.
Supplementary analgesic medicinal products are generally required in addition to Propofol-Lipuro 10 mg/ml.

Posology

Propofol-Lipuro 10 mg/ml is given intravenously. The dosage is adjusted individually according to the patient's response.

- *General anaesthesia in adults*

Induction of general anaesthesia:
For induction of anaesthesia Propofol-Lipuro 10 mg/ml should be titrated (20 – 40 mg of propofol every 10 seconds) against the patient's response until the clinical signs show the onset of anaesthesia. Most adult patients younger than 55 years are likely to require 1.5 to 2.5 mg of propofol per kg body weight.
In patients over this age and in patients of ASA grades III and IV, especially those with impaired cardiac function, the dosage requirements will be less and the total dose of Propofol-Lipuro 10 mg/ml may be reduced to a minimum of 1 mg/kg body weight. In these patients lower rates of administration should be applied (approximately 2 ml, corresponding to 20 mg every 10 seconds).

Maintenance of general anaesthesia:
Anaesthesia can be maintained by administering Propofol-Lipuro 10 mg/ml either by continuous infusion or by repeat bolus injections. If a technique involving repeat bolus injections is used, increments of 25 mg (2.5 ml Propofol-Lipuro 10 mg/ml) to 50 mg (5.0 ml Propofol-Lipuro 10 mg/ml) may be given according to clinical requirements. For maintenance of anaesthesia by continuous infusion the dosage requirements usually are in the range of 4 – 12 mg/kg body weight/h.
In elderly patients, in patients of poor general condition, in patients of ASA grades III and IV and in hypovolaemic patients the dosage may be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.

- *General anaesthesia in children over 1 month*

Induction of anaesthesia:
For induction of anaesthesia Propofol-Lipuro 10 mg/ml should be slowly titrated against the patient's response until the clinical signs show the onset of anaesthesia. The dosage should be adjusted according to age and/or body weight.
Most patients over 8 years of age require approximately 2.5 mg/kg body weight of propofol for induction of anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher (2.5 – 4 mg/kg body weight).

Maintenance of general anaesthesia:
Anaesthesia can be maintained by administering Propofol-Lipuro 10 mg/ml by infusion injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients but rates in the region of 9 – 15 mg/kg/h usually achieve satisfactory anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher.
For ASA III and IV patients lower doses are recommended (see also section 4.4)

- *Sedation of ventilated patients in the Intensive Care Unit*

For sedation during intensive care it is advised that propofol should be administered by continuous infusion. The infusion rate should be determined by the desired depth of sedation. In most patients sufficient sedation can be obtained with a dosage of 0.3 - 4 mg/kg/h of propofol (see also section 4.4).
Propofol is not indicated for sedation in intensive care of patients of 16 years of age or younger (see section 4.3).
Administration of propofol by Target Controlled Infusion (TCI) system is not advised for sedation in the intensive care unit.

- *Sedation for diagnostic and surgical procedures in adults*

To provide sedation during surgical and diagnostic procedures, doses and administration rates should be adjusted according to the clinical response. Most patients will require 0.5 – 1 mg/kg body weight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol-Lipuro 10 mg/ml infusion to the desired level of sedation. Most patients will require 1.5 – 4.5 mg/kg body weight/h. The infusion may be supplemented by bolus administration of 10 – 20 mg (1 – 2 ml Propofol-Lipuro 10 mg/ml) if a rapid increase of the depth of sedation is required.
In patients older than 55 years and in patients of ASA grades III and IV lower doses of Propofol-Lipuro 10 mg/ml may be required and the rate of administration may need to be reduced.
- Propofol-Lipuro 1 % (10 mg/ml) must not be used for sedation for diagnostic and surgical procedures in patients of 16 years or younger.

Method and duration of administration

- *Method of administration*

Intravenous use
Propofol-Lipuro 10 mg/ml is administered intravenously by injection or continuous infusion either undiluted or diluted with 5% w/v glucose solution or 0.9% w/v sodium chloride solution (see also section 6.6).
Containers should be shaken before use.
Before use, the neck of the ampoule or the surface of the rubber stopper of the vial should be cleaned with medicinal alcohol (spray or swabs). After use, tapped containers must be discarded.
Propofol-Lipuro 10 mg/ml contains no antimicrobial preservatives and supports growth of microorganisms. Therefore, Propofol-Lipuro 10 mg/ml is to be drawn up aseptically into a sterile syringe or an infusion set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both Propofol-Lipuro 10 mg/ml and the infusion equipment throughout the infusion period.
Any medicinal products or fluids added to a running Propofol-Lipuro 10 mg/ml infusion must be administered close to the cannula site. If infusion sets with filters are to be used, these must be lipid-permeable.
The contents of one ampoule or one vial of Propofol-Lipuro 10 mg/ml and any syringe containing Propofol-Lipuro 10 mg/ml are for **single use** in **one** patient.

Infusion of undiluted Propofol-Lipuro 10 mg/ml
When administering Propofol-Lipuro 10 mg/ml by continuous infusion, it is recommended that burettes, drop counters, syringe pumps or volumetric infusion pumps, should always be used to control the infusion rates. Any portion of Propofol-Lipuro 10 mg/ml remaining after the end of administration or after replacement of the infusion system must be discarded. As established for the parenteral administration of all kinds of fat emulsions, the duration of continuous infusion of Propofol-Lipuro 10 mg/ml from one infusion system must not exceed 12 hours. The infusion line and the reservoir of Propofol-Lipuro 10 mg/ml must be discarded and replaced after 12 hours at the latest.

Infusion of diluted Propofol-Lipuro 10 mg/ml
For administering infusion of diluted Propofol-Lipuro 10 mg/ml, burettes, drop counters, syringe pumps, or volumetric infusion pumps should always be used to control infusion rates and to avoid the risk of accidentally uncontrolled infusion of large volumes of diluted Propofol-Lipuro 10 mg/ml.
The maximum dilution must not exceed 1 part of Propofol-Lipuro 10 mg/ml with 4 parts of 5% w/v glucose solution or 0.9% w/v sodium chloride solution (minimum concentration 2 mg propofol/ml). The mixture should be prepared aseptically immediately prior to administration and must be used within 6 hours of preparation.
In order to reduce pain on initial injection, Propofol-Lipuro 10 mg/ml may be mixed with preservative-free lidocaine injection 1% (mix 20 parts of Propofol-Lipuro 10 mg/ml with up to 1 part of lidocaine injection 1%).
Before giving the muscle relaxants atracurium or mivacurium subsequent to Propofol-Lipuro 10 mg/ml through the same intravenous line, it is recommended that the line be rinsed prior to administration.
Propofol may also be used by Target Controlled Infusion. Due to the different algorithms available on the market for dosage recommendations please refer to the instructions for use leaflet of the device manufacturer.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

- *Duration of administration*

Propofol-Lipuro 10 mg/ml can be administered for a maximum period of 7 days.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Propofol-Lipuro 10 mg/ml contains soya-bean oil and should not be used in patients who are hypersensitive to peanut or soya.
Propofol-Lipuro 10 mg/ml must not be used in patients of 16 years of age or younger for sedation for intensive care (see section 4.4).

4.4 Special warnings and precautions for use

Propofol should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in Intensive Care).
Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. Propofol should not be administered by the person conducting the diagnostic or surgical procedure.
The abuse of and dependence on propofol, predominantly by health care professionals, have been reported. As with other general anaesthetics, the administration of propofol without airway care may result in fatal respiratory complications.
When propofol is administered for conscious sedation, for surgical and diagnostic procedures, patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.
As with other sedative agents, when propofol is used for sedation during operative procedures, involuntary patient movements may occur. During procedures requiring immobility these movements may be hazardous to the operative site.
An adequate period is needed prior to discharge of the patient to ensure full recovery after use of propofol. Very rarely the use of propofol may be associated with the development of a period of post-operative unconsciousness, which may be accompanied by an increase in muscle tone. This may or may not be preceded by a period of wakefulness. Although recovery is spontaneous, appropriate care of an unconscious patient should be administered.
Propofol induced impairment is not generally detectable beyond 12 hours. The effects of propofol, the procedure, concomitant medications, the age and the condition of the patient should be considered when advising patients on:
- The advisability of being accompanied on leaving the place of administration
- The timing of recommencement of skilled or hazardous tasks such as driving
- The use of other agents that may sedate (e.g. benzodiazepines, opiates, alcohol).

As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients (see also section 4.2).
Propofol clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce propofol clearance
Use of propofol is not recommended with electroconvulsive therapy.
In patients with severe cardiac impairment it is recommended that Propofol-Lipuro 1 % (10 mg/ml) is given with great caution and under intensive monitoring.
Propofol lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic agent before induction or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate or when propofol is used in conjunction with other agents likely to cause bradycardia.
When propofol is administered to an epileptic patient, there may be a risk of convulsion. Before anaesthesia of an epileptic patient, it should be checked that the patient has received the antiepileptic treatment.
Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

Paediatric population

The use of propofol is not recommended in newborn infants <1 month of ageas this patient population has not been fully investigated. Pharmacokinetic data (see section 5.2) indicate that clearance is considerably reduced in neonates and has a very high inter-individual variability. Relative overdose could occur on administering doses recommended for older children and result in severe cardiovascular and respiratory depression.
Propofol must not be used in patients of 16 years of age or younger for sedation for intensive care as the safety and efficacy of propofol for sedation in this age group have not been demonstrated. Although no causal relationship has been established, serious undesirable effects with (back-ground) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular these effects concerned occurrence of metabolic acidosis, hyperlipidemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit (see section 4.3).

Advisory statements concerning Intensive Care Unit management

Use of propofol for ICU sedation has been associated with a constellation of metabolic disturbances and system organ failures that may result in death. Reports have been received of combinations of the following: Metabolic acidosis, Rhabdomyolysis, Hyperkalaemia, Hepatomegaly, Renal failure, Hyperlipidaemia, Cardiac arrhythmia, Brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive Cardiac failure usually unresponsive to inotropic supportive treatment. Combinations of these events have been referred to as the **Propofol infusion syndrome.**
These events were mostly seen in patients with serious head injuries and children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.
The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological agents - vasoconstrictors, steroids, inotropes and/or propofol (usually at dose rates greater than 4 mg/kg/h for more than 48 hours).
Prescribers should be alert to these events in patients with the above risk factors and promptly consider decreasing or stopping the propofol dosage when the above signs develop. All sedative and therapeutic agents used in the intensive care unit (ICU) should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intra-cranial pressure (ICP) should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications. Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h.
Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.
It is recommended that blood lipid levels should be monitored if propofol is administered to patients thought to be at particular risk of fat overload. Administration of propofol should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the propofol formulation; 1.0 ml of Propofol-Lipuro 10 mg/ml contains 0.1 g of fat.
Lipids should be monitored in ICU treatment after 3 days.

Additional precautions

Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anaesthesia, surgery and ICU care. Maintenance of normothermia, provision of carbohydrates and good hydration are recommended for such patients. The early presentations of mitochondrial disease exacerbation and of the 'propofol infusion syndrome' may be similar.

Propofol-Lipuro 10 mg/ml contains no antimicrobial preservatives and supports growth of micro-organisms.
When propofol is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both propofol and infusion equipment throughout the infusion period. Any infusion fluids added to the propofol line must be administered close to the cannula site.
Propofol and any syringe containing propofol are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of propofol must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of propofol and the infusion line must be discarded and replaced as appropriate.

Special warnings/precautions regarding excipients

This medicinal product contains less than 1 mmol (23 mg) sodium in 100 ml, i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Propofol has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of propofol may be required where general anaesthesia or sedation is used as an adjunct to regional anaesthetic techniques.
The concurrent administration of other CNS depressants such as pre-medication drugs, inhalation agents, analgesic agents may add to the sedative, anaesthetic and cardiorespiratory depressant effects of propofol.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of propofol during pregnancy has not been established. Propofol should not be given to pregnant women except when absolutely necessary. Propofol crosses the placenta and can cause neonatal depression. Propofol can, however, be used during an induced abortion.

Breast-feeding
Studies of breast-feeding mothers showed that small quantities of propofol are excreted in human milk. Women should therefore not breastfeed for 24 hours after administration of propofol. Milk produced during this period should be discarded.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after use of propofol.
Propofol induced impairment is not generally detectable beyond 12 hours (please see section 4.4).

4.8 Undesirable effects

Induction and maintenance of anaesthesia or sedation with propofol is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic/sedative agent, such as hypotension. These effects depend on the propofol dose administered but also on the type of premedication and other concomitant medication. The nature, severity and incidence of adverse events observed in patients receiving propofol may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

Table of Adverse Drug Reactions

Undesirable effects are listed according to their frequencies as follows:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable Effects
Immune system disorders:	Very rare	Anaphylaxis up to anaphylactic shock – may include angioedema, bronchospasm, erythema and hypotension
Metabolism and nutritional disorders:	Frequency not known (9)	Metabolic acidosis (5), hyper-kalaemia (5), hyperlipidaemia (5)
Psychiatric disorders:	Frequency not known (9)	Euphoric mood, drug abuse and drug dependence (8)
Nervous system disorders:	Common	Headache during recovery phase
	Rare	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Very rare	Postoperative unconsciousness
	Frequency not known (9)	Involuntary movements
Cardiac disorders:	Common	Bradycardia (1)
	Very rare	Pulmonary oedema
	Frequency not known (9)	Cardiac arrhythmia (5), cardiac failure (5), (7)
Vascular disorders:	Common	Hypotension (2)
Respiratory, thoracic and mediastinal disorders:	Common	Transient apnoea during induction
	Frequency not known (9)	Respiratory depression (dose dependent)
Gastrointestinal disorders:	Common	Nausea and vomiting during recovery phase
	Very rare	Pancreatitis
Hepatobiliary disorders	Frequency not known (9)	Hepatomegaly (5)
Musculoskeletal and connective tissue disorders:	Frequency not known (9)	Rhabdomyolysis (3), (5)
Renal and urinary disorders	Very rare	Discolouration of urine following prolonged administration
	Frequency not known (9)	Renal failure(5)
Reproductive system and breast	Very rare	Sexual disinhibition
General disorders and administration site conditions:	Very common	Local pain on induction (4)
	Uncommon	Injection site thrombosis and injection site phlebitis
	Very rare	Tissue necrosis (10) following accidental extravascular administration (11)
	Frequency not known (9)	Local pain, swelling and inflammation following accidental extravascular administration (11)
Investigations	Frequency not known (9)	Brugada type ECG (5), (6)
Injury, poisoning and procedural complications:	Very rare	Postoperative fever

(1) Serious bradycardias are rare. There have been isolated reports of progression to asystole.
(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of propofol.
(3) Very rare reports of rhabdomyolysis have been received where propofol has been given at doses greater than 4 mg/kg/hr for ICU sedation.
(4) May be minimised by using the larger veins of the forearm and antecubital fossa. With Propofol-Lipuro 10 mg/ml local pain can also be minimised by the co-administration of lidocaine.
(5) Combinations of these events, reported as "Propofol infusion syndrome", may be seen in seriously ill patients who often have multiple risk factors for the development of the events, see section 4.4.
(6) Brugada-type ECG - elevated ST-segment and coved T-wave in ECG.
(7) Rapidly progressive cardiac failure (in some cases with fatal outcome) in adults. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.
(8) Abuse of and drug dependence on propofol, predominantly by health care professionals.
(9) Not known as it cannot be estimated from the available clinical trial data.
(10) Necrosis has been reported where tissue viability has been impaired.
(11) Treatment is symptomatic and may include immobilisation and, if possible, elevation of affected limb, cooling, close observation, consultation of surgeon if necessary.

4.9 Overdose

Symptoms
Accidental overdose is likely to cause cardiorespiratory depression.
Treatment
Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require lowering the patient's head and if severe, use of plasma expanders and pressor agents.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other general anaesthetics, ATC-code: N01AX10.

Mechanism of action, pharmacodynamic effect
After intravenous injection of Propofol-Lipuro 10 mg/ml, onset of the hypnotic effect occurs rapidly. Depending on the rate of injection, the time to induction of anaesthesia is between 30 and 40 seconds. The duration of action after a single bolus administration is short due to the rapid metabolism and excretion (4 – 6 minutes).
With the recommended dosage schedule, a clinically relevant accumulation of propofol after repeated bolus injection or after infusion has not been observed.
Patients recover consciousness rapidly.
Bradycardia and hypotension occasionally occur during induction of anaesthesia probably due to a lack of vagolytic activity. The cardio-circulatory situation usually normalises during maintenance of anaesthesia.
The formulation of propofol in a mixed medium- and long-chain triglyceride emulsion leads to lower concentrations of free medicinal product in the aqueous phase compared to pure long-chain triglyceride emulsions. This difference may explain the reduced pain frequency and intensity observed with Propofol-Lipuro formulations in comparative clinical studies, due to the very low concentration of free propofol.

Paediatric population
Limited studies on the duration of propofol based anaesthesia in children indicate safety and efficacy is unchanged up to duration of 4 hours. Literature evidence of use in children documents use for prolonged procedures without changes in safety or efficacy.

5.2 Pharmacokinetic properties

Distribution
After intravenous administration about 98 % of propofol is bound to plasma protein.
After intravenous bolus administration the initial blood level of propofol declines rapidly due to rapid distribution into different compartments (α-phase). The distribution half-life has been calculated as 2 – 4 minutes.
During elimination the decline of blood levels is slower. The elimination half-life during the β-phase is in the range of 30 to 60 minutes. Subsequently a third deep compartment becomes apparent, representing the re- distribution of propofol from weakly perfused tissue.
The central volume of distribution is in the range of 0.2 – 0.79 l/kg body weight, the steady-state volume of distribution in the range of 1.8 – 5.3 l/kg body weight.

Biotransformation
Propofol is mainly metabolized in the liver to form glucuronides of propofol and glucuronides and sulphate conjugates of its corresponding quinol. All metabolites are inactive.

Elimination
Propofol is rapidly cleared from the body (total clearance approx. 2 l/min). Clearance occurs by metabolism, mainly in the liver, where it is blood flow dependent. Clearance is higher in paediatric patients compared with adults. About 88 % of an administered dose is excreted in the form of metabolites in urine. Only 0.3 % is excreted unchanged in urine.

Paediatric population
After a single dose of 3 mg/kg intravenously, propofol clearance/kg body weight increased with age as follows: Median clearance was considerably lower in neonates < 1 month old (n = 25) (20 ml/kg/min) compared to older children (n = 36, age range 4 months – 7 years). Additionally inter-individual variability was considerable in neonates (range 3.7 – 78 ml/kg/min). Due to this limited trial data that indicates a large variability, no dose recommendations can be given for this age group. Median propofol clearance in older aged children after a single 3 mg/kg bolus was 37.5 ml/min/kg (4-24 months) (n = 8), 38.7 ml/min/kg (11– 43 months) (n = 6), 48 mL/min/kg (1 – 3 years)(n = 12), 28.2 ml/min/kg (4 – 7 years)(n = 10) as compared with 23.6 ml/min/kg in adults (n = 6).

5.3 Preclinical safety data

Preclinical data reveal no specific hazard for humans based on conventional studies on repeated dose toxicity or genotoxicity. Carcinogenicity studies have not been conducted.
Reproductive toxicity studies have shown effects related to pharmacodynamic properties of propofol only at high doses, which will increase post-implantation losses in the F1-generation. Teratogenic effects have not been observed.
In local tolerance studies, intramuscular injection resulted in tissue damage around the injection site.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined,
medium-chain triglycerides,
glycerol,
egg lecithin,
sodium oleate,
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other products except those mentioned in section 6.6.

6.3 Shelf Life

Unopened:
2 years.

After first opening:
To be used immediately.

After dilution according to directions:
Administration of dilution must commence immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze.

6.5 Nature and contents of container

Colourless Type I glass ampoules containing 20 ml of emulsion.
Colourless Type II glass vials sealed with bromobutyl rubber stoppers and aluminium caps containing 20 ml, 50 ml or 100 ml of emulsion.

Pack sizes:
glass ampoules: 10 x 10 ml, 5 x 20 ml
glass vials: 10 x 20 ml, 1 x 50 ml, 10 x 50 ml, 1 x 100 ml, 10 x 100 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handlings

Any unused product or waste material should be disposed of in accordance with local requirements.
Containers should be shaken before use.
For single use only. Any portion of contents remaining after first use must be discarded, see section 4.2.
If two layers can be seen after shaking, the medicinal product should not be used.
Propofol-Lipuro 10 mg/ml should only be mixed with the following products: glucose 50 mg/ml (5% w/v) solution for infusion, sodium chloride 9 mg/ml (0.9% w/v) solution for infusion, and preservative-free lidocaine 10 mg/ml (1%) solution for injection (see section 4.2 "Method and duration of administration" "Infusion of diluted Propofol-Lipuro 10 mg/ml")
Co-administration of Propofol-Lipuro 10 mg/ml together with glucose 50 mg/ml (5% w/v) solution for infusion or sodium chloride 9 mg/ml (0.9% w/v) solution for infusion via a Y-connector close to the injection site is possible.

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