〈附件一〉中文PI

飛樂能 注射劑 0.5 毫克 Flolan Injection 0.5 mg

衛署藥輸字第 000017 號

飛樂能 注射劑 1.5 毫克 Flolan Injection 1.5 mg

衛署藥輸字第 000018 號

【定性及定量組成】

每一小瓶含有無菌、冷凍乾燥的 epoprostenol sodium，相當於 0.5 mg 或 1.5 mg 的 epoprostenol。

【劑型】

凍晶注射劑，含輸注溶液用粉末及溶劑。

- 凍晶乾燥粉末

小瓶內含相當於 0.5 mg epoprostenol 的無菌凍晶乾燥 epoprostenol sodium 或相當於 1.5 mg epoprostenol 的無菌凍晶乾燥 epoprostenol sodium。

粉末為白色或灰白色。

- 溶劑

無菌稀釋劑：50ml 小瓶內含清澈無色無菌稀釋劑。

【臨床特性】

【適應症】

<u>原發性肺動脈高血壓</u>

FLOLAN 也適用為紐約心臟協會(NYHA)功能層級第 III 與第 IV 級之中度至重度原發性肺動脈高血壓(PAH)患者*的長期靜脈輸注治療。

* NYHA 功能層級第 III 級—患者有心血管疾病以及因為疲倦、呼吸困難、氣喘或輕微運動時心悸所導致的體能明顯受限。NYHA 功能層級第 IV 級—

休息時出現衰竭心臟症狀的病患，且最輕微的體能運動也會使其加劇。【劑量與用法】

本藥限由醫師使用

FLOLAN 凍晶乾燥的粉末在使用前必須先行調配。僅可使用此隨附的溶液進行藥物的稀釋。在投藥前或投藥期間，最終輸注溶液必須以 0.22 微米或 0.20 微米的無菌過濾器加以過濾(*請見使用與操作說明*)。

【劑量】

- 成人

原發性肺動脈高血壓

目前已發現下述的使用方式有效。

短期(急性)劑量範圍

必須經由周邊或中央靜脈施以短期劑量範圍探測程序，方可確定長期輸注速率。從 2 ng/kg/min 的輸注速率開始，每 15 分鐘或更長的時間增加 2 ng/kg/min，直到產生最大血液動力學效益或引發劑量限制的藥理學作用為止。

如果病患無法耐受 2 ng/kg/min 的初期輸注速率，應找出病患能夠耐受的更低劑量。

長期連續輸注

應透過中央靜脈導管進行 *FLOLAN* 長期連續輸注。可暫時使用周邊靜脈輸注，直到中央入口建立為止。應以比短期劑量範圍探測期間判定之最大耐受輸注速率低 4 ng/kg/min 的速率開始長期輸注。如果最大耐受輸注速率為 5 ng/kg/min 或更低，則應以 1 ng/kg/min 的速率開始長期輸注。

劑量調整

應以病患肺動脈高血壓症狀的維持、復發或惡化，或是因於 *FLOLAN* 劑量過高所導致的不良反應為基礎，變更長期輸注速率。

一般而言，預計初期的長期劑量應隨著時間而有調高的必要。如果肺動脈高血壓症狀持續或於改善後再復發，則應考慮增加劑量。每次將每分鐘輸注速率增加 1 至 2 ng/kg，應有足夠的時間(間隔時間至少應為 15 分鐘)，以便評估臨床反應。確定新的輸注速率後，應觀察病患，且應監測站立與仰臥血壓及心跳速率數小時，以確保病患可耐受新的劑量。

在長期輸注期間，如果出現與劑量範圍探測期間觀察到之相似的劑量相關藥理學事件，可能需要降低輸注速率。但不良反應有時不需調整劑量也會緩解。可每 15 分鐘或更長時間以降低 2 ng/kg/min 的遞減方式來降低劑量，直到劑量限制作用緩

解為止。應避免突然中斷 *FLOLAN* 或突然大幅降低輸注速率。除非患者有危及生命的情況(例如：失去意識、崩潰等)，否則只能在醫師的指示下才可調整 *FLOLAN* 的輸注速率(*請見警語及注意事項*)。

- 兒童

無在肺動脈高血壓兒童中使用 *FLOLAN* 的資訊。

- 老年人

無在 65 歲以上之肺動脈高血壓病患中使用 *FLOLAN* 的資訊。一般而言，因為老年病患有較高的機率出現肝臟、腎臟(在肺動脈高血壓的情況下)或心臟功能衰退，而且常伴隨其他疾病或其他藥物治療，故應謹慎調節老年病患的劑量。

【禁忌症】

– *FLOLAN* 禁用於對本藥過敏的病患。

– *FLOLAN* 禁用於重度左心室功能不全所導致的鬱血性心臟衰竭。

– *FLOLAN* 不應長期使用於劑量範圍探測期間曾出現肺水腫的病患。

【警語及注意事項】

因為最終輸注溶液 pH 值較高，在給藥時應小心避免藥物外漏，以及伴隨發生的組織損傷風險。

FLOLAN 是一種強效的肺臟與全身性血管擴張劑，輸注期間產生的心血管作用，在投藥結束後 30 分鐘內即會消失。

FLOLAN 是一種強效的血小板聚集抑制劑。因此，應考量出血性併發症風險的增加，尤其是具有其他出血風險的病患(*請見交互作用*)。

如果在 *FLOLAN* 給藥期間出現過度的低血壓，則應減低劑量或停止輸注。劑量過高可能會導致低血壓，嚴重時可能會導致意識喪失(*請見過量*)。

在 *FLOLAN* 給藥期間，應監控血壓與心跳速率。

FLOLAN 可能會降低或增加心跳速率。一般認為此變化取決於基礎心跳速率，以及使用的 *FLOLAN* 濃度。

FLOLAN 對心跳速率的作用可能會因併用影響心血管反射的藥物而被遮蓋。

曾有血清葡萄糖濃度上升的報告。

無菌稀釋劑不含防腐劑，因此一瓶僅可使用一次，之後即應丟棄。

<u>原發性肺動脈高血壓</u>

應避免突然中斷或驟然減少輸注速率之使用，除非是危及生命之情況(例如：失去意識、崩潰等)。突發性的治療中斷可造成反彈性肺動脈高血壓，導致暈眩、無力、增加呼吸困難和可能造成死亡。

只有具有診斷與治療原發性肺動脈高血壓經驗的臨床醫師，才可使用 *FLOLAN*。

必須在有足夠的人力與血液動力學監控與緊急照護設備的醫院環境中，才可進行 *FLOLAN* 短期劑量範圍探測。

有些原發性肺動脈高血壓患者在劑量範圍探測時曾出現肺水腫，這可能與肺部靜脈阻塞疾病有關。

FLOLAN 係透過永久植入的中央靜脈導管，經由小型攜帶式輸注幫浦進行連續輸注。因此，*FLOLAN* 治療需要病患配合無菌藥物調配、藥物投予、照料永久植入的中央靜脈導管，密集且持續性的病患教育。

準備藥物與照料導管時，必須遵守無菌技術。即使短暫中斷 *FLOLAN* 的輸注，也可能導致迅速的症狀惡化。投予 *FLOLAN* 以治療肺動脈高血壓的決定，應以病患瞭解需長期(可能長達數年)使用 *FLOLAN* 治療的高度可能性為基礎，且應仔細考量病患接受及照料永久性靜脈輸注導管及輸注幫浦的能力。

【交互作用】

在同時使用抗凝血劑的病患中投予 *FLOLAN* 時，建議應進行標準化的抗凝血監控。

FLOLAN 的血管擴張作用，可能會增強其他併用之血管擴張劑的作用，也可能被其他併用之血管擴張劑所增強。

如同其他前列腺素類似藥物的報告，*FLOLAN* 可能會增加組織纖維蛋白溶酶原活化劑(t-PA)的肝臟清除率，而降低 t-PA 的血栓溶解作用。

併用 NSAIDS 或其他會影響血小板凝集的藥物時，*FLOLAN* 可能會增加出血的風險。

使用毛地黃的病患，在開始 *FLOLAN* 治療後，可能會出現毛地黃濃度增加，雖然是暫時性，但在容易發生毛地黃中毒的病患，可能產生嚴重的臨床症狀。

【懷孕與授乳】

<u>生殖能力</u>

動物研究並未顯示對生殖能力會造成傷害，但這些動物研究結果與人類的關聯性是未知的(*請見臨床前安全性資料*)。

<u>懷孕</u>

動物研究並未顯示對懷孕、胚胎與胎兒的成長、分娩或產後發展方面會造成傷害，但這些動物研究結果與人類的關聯性是未知的(*請見臨床前安全性資料*)。

在缺乏孕婦使用 *FLOLAN* 足夠的經驗，應權衡對孕婦的潛在效益與對於胎兒的不明風險之利弊。

<u>授乳</u>

目前未知 epoprostenol 或其代謝物是否會分泌至人類乳汁。因此無法排除對餵食母乳孩童之風險。必需決定是否停止/避免餵食母乳或停止/避免 *FLOLAN* 的治療，須考慮餵食母乳對於孩童的效益以及治療對於婦女的效益。

【對駕駛及機械操作能力的影響】

肺動脈高血壓及其治療方式可能會影響駕駛能力與操作機器的能力。

【不良反應】

依系統器官分類與發生頻率將不良反應列於下方。頻率定義如下：極常見≥ 1/10 (≥ 10%)；常見≥ 1/100 與< 1/10 (≥ 1%與< 10%)；少見≥ 1/1000 與< 1/100 (≥ 0.1%與< 1%)；罕見≥ 1/10,000 與< 1/1000 (≥ 0.01%與< 0.1%)；極罕見< 1/10,000 (<0.01%)。

長期使用 *FLOLAN* 所出現的不良反應，會因治療中潛在疾病的臨床特徵而難以解釋。

<u>感染及寄生蟲感染</u>

常見	敗血症、菌血症(大部分與 *FLOLAN* 輸送系統有關)
	曾有不全然具致病性的有機體(包括球菌)引起的導管相關感染被通報。

<u>血液與淋巴系統疾病</u>

常見	血小板數降低、各部位出血(例如：肺部的、胃腸道、鼻出血、顱內的(intracranial)、術後(post-procedural)，腹膜腔後的(retroperitoneal))
極罕見	脾腫大、脾臟功能亢進

<u>內分泌疾病</u>

極罕見	甲狀腺機能亢進

<u>精神疾病</u>

常見	焦慮、神經質
極罕見	躁動

<u>神經系統疾病</u>

極常見	頭痛

<u>心臟疾病</u>

常見	在 5 ng/kg/min 及以下劑量的 *FLOLAN* 中，曾有心搏過速的反應報告。
	心搏過慢，有時會伴隨姿勢性低血壓，曾發生於使用 *FLOLAN* 每分鐘劑量超過 5 ng/kg 的健康受試者中。針對健康清醒受試者靜脈投予相當於每分鐘 30 ng/kg 之 *FLOLAN* 時，曾出現與收縮與舒張壓大幅下降有關的心搏過慢。

<u>血管疾病</u>

極常見	臉部潮紅(即使是在麻醉病患中亦可觀察到)
常見	低血壓
極罕見	[illegible]、蒼白

<u>呼吸道、胸腔及縱膈的疾病</u>

少見	肺水腫

<u>胃腸道疾病</u>

極常見	噁心、嘔吐、腹瀉
常見	腹部絞痛(有時通報為腹部不適)
少見	口乾

<u>皮膚和皮下組織疾病</u>

常見	皮疹

少見	出汗

<u>肌肉骨骼和結締組織疾病</u>

極常見	下巴疼痛
常見	關節痛

<u>一般疾病及注射部位症狀</u>

極常見	疼痛(未細分)
常見	注射處疼痛*、胸痛
少見	局部感染*
極罕見	輸注部位發紅*、長型靜脈導管阻塞*、倦怠、胸悶

*與 *FLOLAN* 的輸送系統有關

【過量】

<u>症狀和徵兆</u>

一般而言，在 *FLOLAN* 過量後出現的事件，係該藥物表現出過度的藥理學作用。(例如：低血壓以及低血壓所造成之併發症)

<u>治療</u>

如果發生劑量過高，則應降低劑量或停止輸注，並視需要展開適當的支持性措施，例如血漿容量擴張和/或調整幫浦流速。

【藥理學特性】

【藥效學】

<u>作用機轉</u>

FLOLAN 是 epoprostenol 的單鈉鹽，epoprostenol 是一種由血管內膜自然形成的前列腺素。Epoprostenol 是目前已知最強的血小板凝集抑制劑，同時也是強效的血管擴張劑。

在人類血小板中 epoprostenol 的許多作用係透過刺激腺苷酸環化酶(adenylate cyclase)而達成，並導致胞內環腺苷單磷酸(cAMP)濃度增加。持續刺激腺苷酸環化酶，進而活化磷酸二酯酶。cAMP 濃度上升會刺激鈣離子排除而調節細胞內鈣離子濃度，

最終並因降低細胞質內鈣離子而抑制血小板凝集(鈣離子濃度決定血小板形狀改變、凝集與釋放反應)。

<u>藥效學影響</u>

持續 30 分鐘每分鐘輸注 4 ng/kg，對心跳速率或血壓並無明顯影響，雖然在此濃度下可能會出現臉部潮紅。

- 原發性肺動脈高血壓

在原發性 PAH (IPAH)族群中，靜脈輸注 *FLOLAN* 15 分鐘，會引起心臟指數(CI)及心搏容積(SV)劑量相關的增加，以及造成肺血管阻力(PVR)、肺循環總阻值(TPR)、平均全身動脈壓(SAPm)劑量相關的下降。*FLOLAN* 對原發性 PAH 之平均肺動脈壓(PAPm)的影響不一且不明顯。

IPAH 患者以 *FLOLAN* 治療 12 週後的慢性血液動力學作用，與在急性試驗中所觀察到的相似。相較於未接受 *FLOLAN* 的患者，長期使用 *FLOLAN* 之病患，其 CI、SV 與動脈氧氣飽和度均增加，PAPm、PVR、平均右心房壓(RAPm)、TPR 與全身血管阻力(SVR)均下降。

【藥物動力學】

因為 *FLOLAN* 的化學性質不穩定，強效且半衰期短，目前並無精準、準確的檢驗可定量生物體液中的 epoprostenol 濃度。

<u>分布</u>

靜脈投予 epoprostenol 會迅速從血液分布至組織。

<u>代謝</u>

在正常的生理 pH 值與溫度下，epoprostenol 會自動分解為 6-oxo-prostaglandin F_1alpha，雖然有些會經酵素降解為其他代謝物。

在人體中使用放射線標定 epoprostenol 後，至少可發現 16 種代謝物，並可辨識其中 10 種的結構。

不同於其他前列腺素，epoprostenol 在通過肺部循環時並未被代謝。

<u>排除</u>

從 epoprostenol 在人體全血中的生體外降解速率推算，預計在男性中自動分解為 6-oxo-prostaglandin F_1alpha 的半衰期不超過 6 分鐘，且可能短至 2 到 3 分鐘。

在人體中使用放射線標定 epoprostenol 後，尿液與糞便的回收率分別為 82%與 4%。

【臨床前安全性資料】

<u>致癌性、致突變性</u>

Epoprostenol 曾以 0、10、20 或 40 mg/kg 分為多次劑量，經腹腔內投予，在安姆氏試驗沙門氏菌檢驗（Ames Salmonella assay）與鹼性析出法（alkaline elution assay）中，進行生體外 DNA 損傷試驗，並在大鼠中進行微核試驗（micronucleus test）。在這三種檢驗中，均無任何基因毒性的徵兆。

目前尚未在動物中進行長期研究，來判定 Epoprostenol 是否有潛在的致癌性。

<u>生殖毒性</u>

在懷孕兔子與大鼠身上使用 epoprostenol 時，已證實並無致畸胎性徵兆。

一項達 74 或 63 天的研究顯示，分別以每天 0、10、30 或 100 μg/kg 皮下投予 epoprostenol 於雄大鼠與雌大鼠，並不會影響其生育力。

曾以大鼠與兔子為對象進行研究，涵蓋其各生殖週期階段，使用高達每天 100 μg/kg 的 epoprostenol 劑量，並未偵測到對於發情、受孕力、妊娠、分娩、哺乳至斷奶的顯著影響。在許多出現產前與產後的檢查中，並無胎兒毒性或致畸胎性的證據，且在留下的後代中，生理與行為發展與受孕力均正常。

<u>動物藥理學</u>

在兔子的藥物動力學研究中，全身分布量為 1015 mL/kg，且全身清除率為每秒 4.27 mL/kg。在靜脈輸注放射線標定之 epoprostenol 後，在肝臟、腎臟、小腸發現最高濃度。在動物輸注中，在 15 分鐘內血漿氚標定的 epoprostenol 濃度即達到穩定狀態，且與輸注速率成比例。血漿濃度會迅速下降，且並無藥物和相關成分累積或長期滯留的證據。

目前已發現 epoprostenol 代謝物在大鼠尿液排泄中，佔使用劑量的 40%，在狗中為 90%，其餘則經由膽道排泄。在兩種物種的尿液排泄中，於投藥後 25 小時內，均可完成超過 95%的排泄。在肌肝的小鼠中，證實有大量的藥品經肝臟清除，且一次循環即移除約 80%的藥物。

【藥劑學特性】

【賦形劑】

凍晶乾燥粉末

Glycine, sodium chloride, mannitol, sodium hydroxide.

無菌稀釋劑

Glycine, sodium chloride, sodium hydroxide, water for injection.

【配伍禁忌】

僅可使用提供的無菌稀釋劑調配 *FLOLAN*，僅可使用建議的溶液來執行任何進一步的稀釋(*請見使用與操作說明*)。

使用 *FLOLAN* 治療原發性肺動脈高血壓時，不可與其他靜脈注射溶液或藥物併用(*請見使用與操作說明*)。

【貯存期】

- 未開封小瓶

有效日期標示於外盒上。

- 調配期間之安定性

<u>治療原發性肺動脈高血壓之</u>調配/使用無菌稀釋劑稀釋溶液

濃度≤150,000 ng/mL：

輸注用之調配後溶液 (濃縮溶液或是已稀釋溶液)，可於調配後立即使用或在輸注前保存於 2-8°C 中最多 8 天。調配後溶液於不同儲存溫度條件之期限如下：

25°C 內：72 小時或

30°C 內：48 小時或

35°C 內：24 小時或

40°C 內：12 小時

任何未使用完之溶液應於過期後丟棄。

溶液>150,000 ng/mL 且≤300,000 ng/mL：

調配後溶液保存於 2-8°C 中最多 7 天，施打時可於 25°C 下最多存放 24 小時。若調配後溶液保存於 2-8°C 中不超過 5 天，施打時可於 25°C 內存放 48 小時；35°C 內存放 24 小時。

任何未使用完之溶液應於過期後丟棄。

【貯存注意事項】

凍晶乾燥粉末

請勿將 *FLOLAN* 小瓶存放於 30°C 以上，避免光線照射，保持乾燥，請勿冷凍。在這些條件下，未開啟小瓶中冷凍乾燥的 *FLOLAN*，並不會受到大氣中的濕氣影響。

無菌稀釋劑

請勿存放於超過 30°C，請勿冷凍，避免光線照射。無菌稀釋劑不含防腐劑，因此一瓶僅可使用一次，並且於使用後丟棄。

【容器的特性及內容物】

凍晶乾燥粉末：

以含氯化丁基橡膠瓶塞和鋁製瓶環密封瓶口的玻璃小瓶中含有冷凍乾燥藥粉。

無菌稀釋劑：

以含氯化丁基橡膠瓶塞和鋁製瓶環密封瓶口且附有紫色掀開式頂蓋的塑膠小瓶中含有無菌稀釋劑。

<u>原發性肺動脈高血壓</u>

一瓶裝有無菌、冷凍乾燥 epoprostenol（含有相當於 0.5 mg 或 1.5 mg 的 epoprostenol）的小瓶，與兩瓶裝有 50 mL 無菌稀釋劑溶液的小瓶及過濾器один置一組供應。

一瓶裝有無菌、冷凍乾燥 epoprostenol（含有相當於 0.5 mg 或 1.5 mg 的 epoprostenol）的小瓶單獨供應。

【使用與操作說明】

FLOLAN 溶液的安定性取決於 pH 值。僅可使用提供的無菌稀釋劑調配冷凍乾燥的 *FLOLAN*，且僅可依註明的比例，使用建議的輸注溶液來執行進一步的稀釋，否則會無法維持必須的 pH 值。

- 調配、稀釋與輸注速率計算

調配與稀釋 *FLOLAN* 必須使用無菌技術，且通常上於臨床使用前才進行。

在準備輸注與計算輸注速率時，應特別注意，應仔細遵循下述程序。

<u>原發性肺動脈高血壓</u>

依照劑量需求，可能使用 0.5 mg 或 1.5 mg 的凍晶乾燥 epoprostenol，搭配無菌稀釋液來調配溶液。

調配：

1. 僅可使用提供的無菌稀釋液進行調配。
2. 抽取約 10 mL 無菌稀釋液至無菌針筒內，將其注入含有 500 μg 冷凍乾燥的 *FLOLAN* 的小瓶中，輕輕搖動使藥粉溶解。
3. 將調配完成的 *FLOLAN* 溶液抽取至針筒，將其重新注入剩餘的無菌稀釋液中，並徹底混合。

此溶液會稱為濃縮溶液

- 以 50 mL 無菌稀釋劑調配含有 0.5 mg epoprostenol 之藥物包時，最終濃度為 10,000 ng/mL。
- 以 50 mL 無菌稀釋劑調配含有 1.5 mg epoprostenol 之藥物包時，最終濃度為 30,000 ng/mL。

稀釋：

FLOLAN 可以使用濃縮液或稀釋劑型作為肺動脈高血壓的治療。僅可使用提供的無菌稀釋劑來稀釋調配 *FLOLAN*。使用 *FLOLAN* 治療肺動脈高血壓時，不可使用生理食鹽水。

治療原發性肺動脈高血壓時，*FLOLAN* 不得與其他靜脈注射溶液或藥物一起使用。

準備為病患輸注的最終溶液必須使用 0.22 或 0.20 微米的過濾器加以過濾。最好是在輸注期間使用輸注裝置中所裝配的管線內過濾器。或者，如果無法進行管線內過濾，則必須在貯入藥匣之前將最終溶液(濃縮或進一步稀釋後的溶液)以所提供的 0.20 微米無菌過濾器加以過濾。

如果是在輸注期間使用管線內過濾器，在替換輸注裝置時即應將此管線內過濾器丟棄。

如果是在準備藥物期間使用針筒過濾器，該針筒過濾器僅可於準備藥物期間使用，然後就應丟棄。

輸注速率的計算：

治療原發性肺動脈高血壓的常用濃度如下：

- 15,000 ng/mL－以無菌稀釋劑調配 1.5 mg epoprostenol 並稀釋至總體積為 100 mL。
- 10,000 ng/mL－調配兩瓶含有 0.5 mg epoprostenol 的藥瓶，並稀釋至總體積為 100 mL。
- 5,000 ng/mL－調配一瓶含有 0.5 mg epoprostenol 的藥瓶，並稀釋至總體積為 100 mL。

以下列公式計算輸注速率：

$$\underset{(\text{mL/min})}{\text{輸注速率}} = \frac{\text{每分鐘劑量(ng/kg)} \times \text{體重(kg)}}{\text{溶液濃度(ng/mL)}}$$

$$\text{輸注速率(mL/h)} = \text{輸注速率(mL/min)} \times 60$$

以下為原發性肺動脈高血壓常用的一些濃度範例。

濃度 15,000 ng/mL 的輸注速率：

每分鐘劑量 (ng/kg)	體重(公斤)							
	30	40	50	60	70	80	90	100
4				1.0	1.1	1.3	1.4	1.6
6		1.0	1.2	1.4	1.7	1.9	2.2	2.4
8	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2
10	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0
12	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
14	1.7	2.2	2.8	3.4	3.9	4.5	5.0	5.6
16	1.9	2.6	3.2	3.8	4.5	5.1	5.8	6.4
	以毫升/小時（mL/h）為單位的速度							

濃度 5,000 ng/mL 的輸注速率：

每分鐘劑量 (ng/kg)	體重(公斤)									
	10	20	30	40	50	60	70	80	90	100
2				1.0	1.2	1.4	1.7	1.9	2.2	2.4
4		1.0	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
6		1.4	2.2	2.9	3.6	4.3	5.0	5.8	6.5	7.2
8	1.0	1.9	2.9	3.8	4.8	5.8	6.7	7.7	8.6	9.6
10	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
12	1.4	2.9	4.3	5.8	7.2	8.6	10.1	11.5	13.0	14.4
14	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4	15.1	16.8
16	1.9	3.8	5.8	7.7	9.6	11.5	13.4	15.4	17.3	19.2
	以毫升/小時為（mL/h）單位的速度									

版本編號：GDS27/IPI14
版本日期：2016 年 10 月 10 日

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<附件一> 英文PI

FLOLAN

epoprostenol sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vials containing sterile, freeze-dried epoprostenol sodium equivalent to *0.5 mg* or 1.5 mg epoprostenol.

PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

Freeze-dried powder

- *Vials containing sterile, freeze-dried epoprostenol sodium equivalent to 0.5 mg epoprostenol, or*
- *Vials containing sterile, freeze-dried epoprostenol sodium equivalent to 1.5 mg epoprostenol.*

The powder is white or off-white.

Solvent

- *Sterile diluent*

50ml. vials containing sterile diluent to reconstitute freeze-dried powders: clear, colourless solution.

CLINICAL PARTICULARS

Indications

Primary Pulmonary Arterial Hypertension

FLOLAN is also indicated for the long-term i.v. treatment of moderate to severe primary pulmonary arterial hypertension (PAH) in New York Heart Association (NYHA) functional Class III and Class IV patients*.

* NYHA Functional Class III - patients with cardiovascular disease and marked limitation of physical ability due to the development of pain, dyspnoea, fatigue or

palpitation on mild exertion. NYHA Functional Class IV – patients with the above cardiac symptoms at rest, which are made worse by the slightest physical exertion.

Dosage and Administration

FLOLAN lyophilised powder must be reconstituted before use. Any further dilution must be performed using only the recommended solutions. The final infusion solution must be filtered with a sterile 0.22 micron or 0.20 micron filter prior to or during administration *(see Instructions for Use/Handling)*.

Populations

- Adults

Primary Pulmonary Arterial Hypertension

The following schedules have been found effective.

Short-term (acute) dose ranging

A short-term dose-ranging procedure administered via either a peripheral or central venous line is required to determine the long-term infusion rate. The infusion rate is initiated at 2 nanograms/kg/min and increased by increments of 2 nanograms/kg/min every 15 minutes or longer until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited.

If the initial infusion rate of 2 nanograms/kg/min is not tolerated, a lower dose which is tolerated by the patient should be identified.

Long-term continuous infusion

Long-term continuous infusion of *FLOLAN* should be administered through a central venous catheter. Temporary peripheral i.v. infusions may be used until central access is established. Long-term infusions should be initiated at 4 nanograms/kg/min less than the maximum tolerated infusion rate determined during short-term dose-ranging. If the maximum tolerated infusion rate is 5 nanograms/kg/min or less, then the long-term infusion should be started at 1 nanogram/kg/min.

Dosage adjustments

Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of pulmonary arterial hypertension or the occurrence of adverse events due to excessive doses of *FLOLAN*.

In general, the need for increases in dose from the initial long-term dose should be expected over time. Increases in dose should be considered if symptoms of pulmonary arterial hypertension persist, or recur after improving. The infusion rate should be increased by 1 to 2 nanograms/kg/min increments at intervals sufficient to allow

assessment of clinical response; these intervals should be of at least 15 minutes. Following establishment of a new infusion rate, the patient should be observed, and sitting and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During long-term infusion, the occurrence of dose-related pharmacological events similar to those observed during the dose-ranging period may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2 nanograms/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Abrupt withdrawal of *FLOLAN* or sudden large reductions in infusion rates should be avoided. Except in life-threatening situations (e.g. unconsciousness, collapse, etc) infusion rates of *FLOLAN* should be adjusted only under the direction of a physician *(see Warnings and Precautions)*.

- Children

There is no specific information on the use of *FLOLAN* for pulmonary arterial hypertension in children.

- Elderly

There is no specific information on the use of *FLOLAN* in patients over 65 for pulmonary arterial hypertension. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal (in the case of pulmonary arterial hypertension) or cardiac function and of concomitant disease or other drug therapy.

Contraindications

- *FLOLAN* is contraindicated in patients with known hypersensitivity to the drug.
- *FLOLAN* is contraindicated in patients with congestive heart failure arising from severe left ventricular dysfunction.
- *FLOLAN* should not be used chronically in patients who develop pulmonary oedema during dose-ranging.

Warnings and Precautions

Because of the high pH of the final infusion solutions, care should be taken to avoid extravasation during their administration and consequent risk of tissue damage.

FLOLAN is a potent pulmonary and systemic vasodilator. The cardiovascular effects during infusion disappear within 30 minutes of the end of administration.

FLOLAN is a potent inhibitor of platelet aggregation, therefore, an increased risk for haemorrhagic complications should be considered, particularly for patients with other risk factors for bleeding (see Interactions).

If excessive hypotension occurs during administration of *FLOLAN*, the dose should be reduced or the infusion discontinued. Hypotension may be profound in overdose and may result in loss of consciousness *(see Overdose)*.

Blood pressure and heart rate should be monitored during administration of *FLOLAN*.

FLOLAN may either decrease or increase heart rate. The change is thought to depend on both the basal heart rate and the concentration of *FLOLAN* administered.

The effects of *FLOLAN* on heart rate may be masked by concomitant use of drugs which affect cardiovascular reflexes.

Elevated serum glucose levels have been reported.

Sterile diluent contains no preservative, consequently a vial should be used once only and then discarded.

Primary Pulmonary Arterial Hypertension

Abrupt withdrawal or interruption of infusion must be avoided, except in life-threatening situations (e.g. unconsciousness, collapse, etc). An abrupt interruption of therapy can induce a rebound of pulmonary arterial hypertension resulting in dizziness, asthenia, increased dyspnoea, and may lead to death.

FLOLAN should be used only by clinicians experienced in the diagnosis and treatment of these disorders.

Short-term dose-ranging with *FLOLAN* must be performed in a hospital setting with adequate personnel and equipment for haemodynamic monitoring and emergency care.

Some patients with primary pulmonary arterial hypertension have developed pulmonary oedema during dose-ranging, which may be associated with pulmonary veno-occlusive disease.

FLOLAN is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with *FLOLAN* requires commitment by the patient to sterile drug reconstitution, drug administration, care of the permanent central venous catheter, and access to intense and ongoing patient education.

Sterile technique must be adhered to in preparing the drug and in the care of the catheter. Even brief interruptions in the delivery of *FLOLAN* may result in rapid symptomatic deterioration. The decision to administer *FLOLAN* for pulmonary arterial hypertension should be based upon the patient's understanding that there is a high likelihood that therapy with *FLOLAN* will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent i.v. catheter and infusion pump should be carefully considered.

Interactions

When *FLOLAN* is administered to patients receiving concomitant anticoagulants standard anticoagulant monitoring is advisable.

The vasodilator effects of *FLOLAN* may augment or be augmented by concomitant use of other vasodilators.

As reported with other prostaglandin analogues, *FLOLAN* may reduce the thrombolytic efficacy of tissue plasminogen activator (t-PA) by increasing hepatic clearance of t-PA.

When NSAIDS or other drugs affecting platelet aggregation are used concomitantly, there is the potential for *FLOLAN* to increase the risk of bleeding.

Patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with *FLOLAN*, which although transient, may be clinically significant in patients prone to digoxin toxicity.

Pregnancy and Lactation

Fertility

Animal studies did not indicate harmful effects with respect to fertility. However, the relevance of these animal findings in man is unknown *(see Pre-clinical Safety Data)*.

Pregnancy

Animal studies did not indicate harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. However, the relevance of these findings in man is unknown *(see Pre-clinical Safety Data)*.

In the absence of adequate experience of administration of *FLOLAN* to pregnant women, the potential benefit to the mother must be weighed against the unknown risks to the foetus.

Lactation

It is unknown if epoprostenol or its metabolites are excreted in human milk. A risk to the breast-feeding child can not be excluded. A decision must be made whether to discontinue/abstain from breast-feeding or to discontinue/abstain from *FLOLAN* therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Effects on Ability to Drive and Use Machines

Pulmonary arterial hypertension and its therapeutic management may affect the ability to drive and operate machinery.

Adverse Reactions

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common ≥1/10 (≥10%); common ≥1/100 and <1/10 (≥1% and <10%); uncommon ≥1/1000 and <1/100 (≥0.1% and <1%); rare ≥1/10,000 and <1/1000 (≥0.01% and <0.1%); very rare <1/10,000 (< 0.01%).

The interpretation of adverse reactions during long term administration of *FLOLAN* is complicated by the clinical features of the underlying disease being treated.

Infections and Infestations	
Common	Sepsis, septicaemia (mostly related to delivery system for *FLOLAN*)
	Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus) have been reported.
Blood and Lymphatic System Disorders	
Common	Decreased platelet count, bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal)
Very rare	Splenomegaly, Hypersplenism
Endocrine Disorders	
Very rare	Hyperthyroidism
Psychiatric Disorders	
Common	Anxiety, nervousness
Very rare	Agitation
Nervous System Disorders	
Very common	Headache
Cardiac Disorders	
Common	Tachycardia has been reported as a response to *FLOLAN* at doses of 5 nanograms/kg/min and below.

	Bradycardia, sometimes accompanied by orthostatic hypotension, has occurred in healthy volunteers at doses of *FLOLAN* greater than 5 nanograms/kg/min. Bradycardia associated with a considerable fall in systolic and diastolic blood pressure has followed i.v. administration of a dose of *FLOLAN* equivalent to 10 nanograms/kg/min in healthy conscious volunteers.
Vascular Disorders	
Very common	Facial flushing (seen even in the anesthetised patient)
Common	Hypotension
Very rare	Ascites, pallor
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Pulmonary oedema
Gastrointestinal Disorders	
Very common	Nausea, vomiting, diarrhoea
Common	Abdominal colic (sometimes reported as abdominal discomfort)
Uncommon	Dry mouth
Skin and Subcutaneous Tissue Disorders	
Common	Rash
Uncommon	Sweating
Musculoskeletal and Connective Tissue Disorders	
Very common	Jaw pain
Common	Arthralgia
General Disorders and Administration Site Conditions	
Very common	Pain (unspecified)
Common	Pain at the injection site*, chest pain
Rare	Local infection*

Very rare	Reddening over the infusion site*, occlusion of the long i.v. catheter*, lassitude, chest tightness

* Associated with the delivery system for *FLOLAN*

Overdose

Symptoms and Signs

In general, events seen after overdose of *FLOLAN* represent exaggerated pharmacological effects of the drug (e.g. hypotension and complications of hypotension).

Treatment

If overdose occurs reduce the dose or discontinue the infusion and initiate appropriate supportive measures as necessary, for example plasma volume expansion and/or adjustment to pump flow.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action

FLOLAN is the monosodium salt of epoprostenol, a naturally occurring prostaglandin produced by the intima of blood vessels. Epoprostenol is the most potent inhibitor of platelet aggregation known. It is also a potent vasodilator.

Many of the actions of epoprostenol are exerted via the stimulation of adenylate cyclase, which leads to increased intracellular levels of cyclic adenosine 3'5' monophosphate (cAMP). A sequential stimulation of adenylate cyclase, followed by activation of phosphodiesterase, has been described in human platelets. Elevated cAMP levels regulate intracellular calcium concentrations by stimulating calcium removal, and thus platelet aggregation is ultimately inhibited by the reduction of cytoplasmic calcium, upon which platelet shape change, aggregation and the release reaction depend.

Pharmacodynamic Effects

Infusions of 4 nanograms/kg/min for 30 minutes have been shown to have no significant effect on heart rate or blood pressure, although facial flushing may occur at these levels.

Primary Pulmonary Arterial Hypertension

Intravenous *FLOLAN* infusions of up to 15 minutes in the idiopathic PAH (IPAH) population have been found to produce dose-related increases in cardiac index (CI) and stroke volume (SV), and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR), and mean systemic arterial pressure (SAPm). The

effects of *FLOLAN* on mean pulmonary artery pressure (PAPm) in patients with IPAH were variable and minor.

Chronic haemodynamic effects after 12 weeks of *FLOLAN* therapy in IPAH, were generally similar to those observed during acute administration. CI, SV, and arterial oxygen saturation were increased, and PAPm, PVR, mean right atrial pressure (RAPm), TPR, and systemic vascular resistance (SVR) were decreased in patients who received *FLOLAN* chronically compared with those who did not.

Pharmacokinetics

Due to the chemical instability, high potency and short half-life of *FLOLAN*, no precise and accurate assay has been identified for quantifying epoprostenol in biological fluids.

Distribution

Intravenously administered epoprostenol is rapidly distributed from blood to tissue.

Metabolism

At normal physiological pH and temperature, epoprostenol breaks down spontaneously to 6-oxo-prostaglandin F_1alpha, although there is some enzymatic degradation to other products.

Following the administration of radiolabelled epoprostenol to humans, at least 16 metabolites were found, 10 of which were structurally identified.

Unlike many other prostaglandins, epoprostenol is not metabolised during passage through the pulmonary circulation.

Elimination

The half-life for the spontaneous breakdown to 6-oxo-prostaglandin F_1alpha in man is expected to be no more than 6 minutes, and may be as short as 2 to 3 minutes, as estimated from in vitro rates of degradation of epoprostenol in human whole blood.

Following the administration of radiolabelled epoprostenol to humans, the urinary and faecal recoveries of radioactivity were 82% and 4%, respectively.

Pre-clinical Safety Data

Carcinogenesis, Mutagenesis

Epoprostenol was tested in vitro in an Ames Salmonella assay and in an alkaline elution assay for DNA damage, and in micronucleus test on rats, at 0, 10, 20 or 40mg/kg, in divided doses by the intraperitoneal route. There were no signs of genotoxicity in any of these three assays.

No long-term studies have been conducted in animals to determine whether epoprostenol is a potential carcinogen.

Reproductive toxicology

Epoprostenol has shown no signs of teratogenicity when administered to pregnant rabbits and rats.

A study in which male and female rats were dosed subcutaneously for 74 or 63 days respectively, with 0, 10, 30 or 100 micrograms/kg/day, showed no effects on fertility.

Studies which between them, cover all stages of the reproductive cycle, using epoprostenol doses of up to 100 micrograms/kg/day, have been conducted in rats and rabbits. No significant effects were detected on oestrus, fertility, gestation, parturition and lactation through to weaning. In litters examined pre- and post-partum, there was no evidence of foetal toxicity or teratogenicity and in maintained offspring, physical and behavioural development and fertility were normal.

Animal pharmacology

A pharmacokinetic study in rabbits showed the whole body distribution to be 1015 mL/kg, and the whole body clearance to be 4.27 mL/kg/sec. Following i.v. injection of radiolabelled epoprostenol, the highest concentrations have been found in the liver, kidneys and small intestine. During infusions in animals, steady-state plasma concentrations of tritium-labelled epoprostenol were reached within 15 minutes and were proportional to infusion rates. Tissue levels decline rapidly with no evidence for accumulation or long-term retention of a drug-related compound.

Urinary excretion of the metabolites of epoprostenol has been found to account for 40% of the administered dose in rats, and 90% in dogs, with biliary excretion accounting for the remainder. In both species urinary excretion was greater than 95% complete within 25 hours of dosing. In anaesthetised dogs extensive clearance by the liver has been demonstrated, with approximately 80% being recovered in a single pass

PHARMACEUTICAL PARTICULARS

List of Excipients

Freeze-dried powder

Glycine, sodium chloride, mannitol, sodium hydroxide.

Sterile diluent
Glycine, sodium chloride, sodium hydroxide, water for injection.

Depending on the dosage required, either 0.5 mg or 1.5 mg freeze-dried epoprostenol may be used for reconstitution with the sterile diluent. **Reconstitution:**

1. Use only the sterile buffer solution provided for reconstitution.
2. Withdraw approximately 10 mL of the sterile buffer solution into a sterile syringe, inject it into the vial containing 500 micrograms freeze-dried *FLOLAN* and shake gently until the powder has dissolved.
3. Draw up the resulting *FLOLAN* solution into the syringe, re-inject it into the remaining volume of the sterile buffer solution and mix thoroughly.

This solution is now referred to as the concentrated solution.

- ***Where a pack containing 0.5 mg epoprostenol is reconstituted with 50 mL sterile diluent the resultant concentration is 10,000 nanograms/mL epoprostenol.***
- Where a pack containing 1.5 mg *epoprostenol* is reconstituted with 50 mL sterile diluent the resultant concentration is 30,000 nanograms/mL.

Higher concentrations may be prepared for patients who receive epoprostenol long term.

Only concentrated solutions are suitable for further dilution with the sterile diluent prior to use.

Dilution:

FLOLAN may be used either as concentrated solution or in a diluted form for the treatment of pulmonary arterial hypertension. Only the sterile diluent provided may be used for the further dilution of reconstituted *FLOLAN*. Physiological saline must not be used when *FLOLAN* is to be used for the treatment of pulmonary arterial hypertension.

FLOLAN must not be administered with other parenteral solutions or medications when used for primary pulmonary arterial hypertension.

The final solution to be administered to the patient must be filtered using a 0.22 or 0.20 micron filter. Use of an in-line filter as part of the infusion set during administration is preferable. Alternatively, where in-line filtration is not possible, the final solution (either a concentrated or further diluted solution) must be filtered with the provided sterile 0.22 micron filter prior to storage in the medication cassette.

If an in-line filter has been used during administration, then the in-line filter should be discarded when the infusion set is exchanged.

If manual syringe filter has been used during preparation, the syringe filter unit must be used only during preparation and then discarded.

Calculation of infusion rate:

Concentrations commonly used in the treatment of pulmonary arterial hypertension are as follows:

- ***15,000 nanograms/mL – 1.5 mg epoprostenol reconstituted and diluted to a total volume of 100mL in sterile diluent***
- ***10,000 nanograms/mL – Two vials containing 0.5 mg epoprostenol reconstituted and diluted to a total volume of 100 mL.***
- ***5,000 nanograms/mL – One vial containing 0.5 mg epoprostenol reconstituted and diluted to a total volume of 100 mL.***

The infusion rate may be calculated from the following formula:

$$\text{Infusion rate} = \frac{\text{dosage (nanograms/kg/min) x bodyweight (kg)}}{\text{concentration of solution (nanograms/mL)}}$$
(mL/min)

Infusion rate (mL/h) = Infusion rate (mL/min) x 60

Examples for some concentrations commonly used in primary pulmonary arterial hypertension are below.

Infusion rates for a concentration of 15,000 nanograms/mL:

Dosage (nanograms/kg/min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
4				1.0	1.1	1.3	1.4	1.6
6		1.0	1.2	1.4	1.7	1.9	2.2	2.4
8	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2
10	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0
12	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
14	1.7	2.2	2.8	3.4	3.9	4.5	5.0	5.6
16	1.9	2.6	3.2	3.8	4.5	5.1	5.8	6.4
	Flow rates in mL/h							

Infusion rates for a concentration of 5,000 nanograms/mL:

Dosage (nanograms/kg/min)	Bodyweight (kg)									
	10	20	30	40	50	60	70	80	90	100
2				1.0	1.2	1.4	1.7	1.9	2.2	2.4
4		1.0	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8

Incompatibilities

FLOLAN must be reconstituted using only the sterile *diluent* provided. Any further dilution must be performed using only the recommended solutions *(see Instructions for Use/Handling)*.

FLOLAN must not be administered with other parenteral solutions or medications when used for primary pulmonary arterial hypertension *(see Instructions for Use/Handling)*.

Shelf Life

Unopened vials

The expiry date is indicated on the packaging.

Stability during administration

Reconstituted/diluted solutions using sterile diluent for pulmonary arterial hypertension

For solutions ≤ 150,000 ng/mL:

Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for up to 8 days at 2°C to 8°C prior to administration. Following this preparation or storage, the solution for infusion should be used within:

- ***72 hours at up to 25°C or***
- ***48 hours at up to 30°C or***
- ***24 hours at up to 35 °C or***
- ***12 hours at up to 40 °C***

Discard any unused solution after this time.

For solutions >150,000ng/mL and ≤300,000ng/mL:

Reconstituted solutions that have been stored at 2 to 8°C for up to 7 days can be administered for up to 24 hours at 25°C.

Freshly prepared reconstituted solutions, or solutions that have been stored at 2 to 8°C for no longer than 5 days can be administered for up to:

- ***48 hours at up to 25°C***
- ***24 hours at up to 35°C***

Discard any unused solution after this time.

Special Precautions for Storage

Freeze-dried powder

Do not store *FLOLAN* vials above 25°C. Protect from light. Keep dry. Do not freeze. Under these conditions, freeze-dried *FLOLAN* in an unopened vial should not be affected by moisture present in the atmosphere.

Sterile diluent

Do not store above 25°C. Do not freeze. Protect from light. ***Sterile*** diluent contains no preservative, consequently a vial should be used once only and then discarded.

Nature and Contents of Container

Freeze-dried powder

The freeze-dried powder is contained in glass vials with synthetic butyl rubber plugs and aluminium collars.

Sterile diluent

The sterile diluent is contained in plastic vials with synthetic butyl rubber plugs and aluminium collars with a purple flip-top cover.

Primary Pulmonary Arterial Hypertension

One vial containing sterile, freeze-dried epoprostenol equivalent to 0.5 mg or 1.5 mg epoprostenol, supplied with two 50 mL vials of sterile *diluent* and a filter unit.

One vial containing sterile, freeze-dried epoprostenol equivalent to 0.5 mg or 1.5 mg epoprostenol supplied alone.

Instructions for Use/Handling

The stability of solutions of *FLOLAN* is pH dependent. Only the *sterile* diluent supplied should be used for reconstitution of freeze-dried *FLOLAN* and only the recommended infusion solutions, in the stated ratio, should be used for further dilution, otherwise the required pH may not be maintained.

- Reconstitution, dilution and calculation of infusion rate

Reconstitution and dilution of *FLOLAN* must be carried out *using aseptic technique, ideally* immediately prior to clinical use.

Particular care should be taken in the preparation of the infusion and in calculating the rate of infusion. The procedure given below should be closely followed.

Primary Pulmonary Arterial Hypertension

6		1.4	2.2	2.9	3.6	4.3	5.0	5.8	6.5	7.2
8	1.0	1.9	2.9	3.8	4.8	5.8	6.7	7.7	8.6	9.6
10	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
12	1.4	2.9	4.3	5.8	7.2	8.6	10.1	11.5	12.9	14.4
14	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4	15.1	16.8
16	1.9	3.8	5.8	7.7	9.6	11.5	13.4	15.4	17.3	19.2
	Flow rates in mL/h									

Version number: GDS27 / IPI14

Date of issue: 10 October 2016

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