

# 디비엘 류코보린 주 (류코보린칼슘) DBL Leucovorin calcium Inj.

## ■원료약품의 분량

- 디비엘 류코보린 주 15mg :  
1앰플(2ml) 중  
<주 성 분> 류코보린칼슘 (유에스피) ..... 16.2 mg  
(류코보린으로서 15mg)  
<용 제> 주사용수(비피) ..... 적량
- 디비엘 류코보린 주 50, 100, 300mg :  
1ml 중  
<주 성 분> 류코보린칼슘 (칼슘폴리네이트)(유에스피) ..... 10.8 mg  
(류코보린으로서 10mg)  
<용 제> 주사용수(비피) ..... 적량

## ■성 상

- 디비엘 류코보린 주 15mg : 갈색의 앰플에 충전된 담황색의 투명한 주사액
- 디비엘 류코보린 주 50, 100, 300mg : 갈색의 바이알에 충전된 담황색의 투명한 주사액

## ■효능 · 효과

1. 엽산대사길항제의 독성 경감
2. 진행성대장암에서의 5-Fluorouracil(5-FU)과의 병용투여

## ■용법 · 용량

1. 메토포렉세이트 통상요법 : 메토포렉세이트(엽산길항제)의 통상 투여량으로 이상 반응이 발현되었을 경우, 폴리네이트로서 1회 6-12mg을 6시간마다 1일 4회 근육 주사한다. 또 메토포렉세이트를 과량투여한 경우에는 투여한 메토포렉세이트와 동량을 투여한다.
2. 메토포렉세이트 · 폴리네이트 구원요법 : 메토포렉세이트 투여종료 후 3시간 후부터 폴리네이트로서 1회 15mg을 3시간마다 9회 정맥주사하고, 이후 6시간마다 8회 정맥 주사 또는 근육주사한다. 메토포렉세이트에 의하는 것으로 생각되는 중증의 이상 반응이 나타나는 경우에는 용량을 증가하고, 투여기간을 연장한다.
3. 진행성대장암에서의 5-Fluorouracil(5-FU)과의 병용투여 : 두가지 요법 중 선택한다.
  - 1) 1일 폴리네이트칼슘 200mg/m<sup>2</sup>을 최소 3분 이상 천천히 정맥주사하고 계속해서 5-FU 370mg/m<sup>2</sup>을 정맥주사한다.
  - 2) 1일 폴리네이트칼슘 20mg/m<sup>2</sup>를 정맥주사하고 계속해서 5-FU 425mg/m<sup>2</sup>를 정맥주사한다. 이 때 5-FU와 폴리네이트의 침전이 형성될 수 있으므로 동시투여 하지 않는다. 위의 치료를 5일동안 계속하고, 이를 4주 간격으로 반복한다.

## ■사용상의 주의사항

1. 경 고
  - 1) 이 약은 비타민 B<sub>12</sub>의 결핍에 의한 악성빈혈과 다른 거대적혈모구빈혈치료에 부적당하다. 신경학적인 증상이 계속 진행되는 동안에도 혈액학적 차도가 일어날 수 있다.
  - 2) 앰플주사제는 용기 절단시 유리파편이 혼입되어, 이상반응을 초래할 수 있으므로 사용시 유리파편 혼입이 최소화될 수 있도록 신중하게 절단사용하되, 특히 어린이, 노약자 사용시에는 각별히 주의한다.
2. 다음 환자에는 투여하지 말 것  
임부 및 수유부(5-FU와의 병용투여에 한함)
3. 다음 환자에는 신중히 투여할 것  
임부 및 수유부(엽산길항제의 독성경감에 투여시)
4. 이상반응
  - 1) 과민증 : 아나필락시양 반응, 두드러기 등이 나타날 수 있다.
  - 2) 투여부위 : 혈관통(정맥주사시), 일과성 동통(근육주사시)이 나타날 수 있다.
  - 3) 발열이 나타날 수 있다.
  - 4) 정신신경계 : 중추신경계장애(마비성장애, 흥분, 우울)이 나타날 수 있다.
  - 5) 5-FU와 병용시 복용배합에 따라 설사, 피부반응, 피부건조, 구내염, 결막염, 점막염, 약한혈액독성, 백혈구감소증이 나타날 수 있다. 심한 설사가 있는 경우 5-FU의 감량을 고려한다.
5. 일반적 주의
  - 1) 이 약은 화학요법제 사용에 경험이 있는 의사의 지시에 따라 메토포렉세이트와 함께 사용되어야 한다.
  - 2) 엽산길항제의 과량투여의 치료에서 이 약은 가능한 즉시 투여되어야 한다. 메토포렉세이트 투여와 폴리네이트칼슘으로의 치료 사이의 시간간격이 증가될수록 독성경감에서 이 약의 유효성이 감소된다.
  - 3) 이 약의 치료기간과 최적용량을 결정하기 위해 혈청 메토포렉세이트농도를 측정한다. 복수나 복막삼출증과 같은 제3의 공간에 액이 축적될 경우나 신부전, 비정상적 수화현상은 메토포렉세이트 배설지연의 원인이 될 수 있다. 그런 경우에는 고용량의 폴리네이트칼슘을 정맥주사로 투여한다.
  - 4) 이 약은 메토포렉세이트와 같은 운반체계를 공유하므로 막운반감소로 인하여 메토포렉세이트에 내성인 경우 이 약에 대해서도 내성임을 의미한다. 환자가 이 약을 흡수할 수 없거나 구토의 가능성이 있으면 엽산저해제 투여 후 이 약의 비경구 투여가 바람직하다. 또한 경구사용 권장량보다 높은 용량은 정맥주사한다.

- 5) 특히 중추신경계종양에서 이 약의 반복투여로 이 약이 축적되어 메토틀렉세이트의 항암효과를 약화시키므로 과량투여를 피한다.
- 6) 이 약은 DNA합성저해제(예 : 히드록시카바미드, 시타라빈, 메르캅토프린, 치오구아닌)에 의한 큰적혈구증가증의 치료에는 사용하지 않는다.
- 7) 이 약은 메토틀렉세이트에 의한 혈액독성외의 이상반응(예 : 신독성)에는 효력이 없다.
- 8) 이 약의 5-FU와의 병용시 임상검사
  - ① 각 투여 전에 혈소판과 감별CBC를 실시한다. 처음 2회동안 주마다 반복하고 각회에 1회 WBC nadir이 예상되는 시점에 실시한다.
  - ② 전해질과 간기능검사를 처음 3회 동안은 각 투여전에 실시하고 그 다음부터 2회에 한 번 투여전에 실시한다.
  - ③ 5-FU의 용량은 이상반응의 심각성에 근거해 다음과 같이 변경한다.

| 검사 and/or 구내염 | WBC/ $\text{mm}^3$<br>Nadir | Platelets/ $\text{mm}^3$<br>Nadir | 5-Fluorouracil<br>Dose |
|---------------|-----------------------------|-----------------------------------|------------------------|
| Moderate      | 1,000 ~ 1,900               | 25 ~ 75,000                       | 20% 감소                 |
| Severe        | < 1,000                     | < 25,000                          | 30% 감소                 |

만일 이상반응이 없으면 5-FU 용량은 10% 증가할 수 있다. 치료는 WBCs 4,000/ $\text{mm}^3$ , 혈소판수 130,000/ $\text{mm}^3$ 가 될 때까지 연장되어야 한다. 만약 혈액치가 2주안에 이 수치에 도달하지 않으면 치료는 중단해야 한다. 각 치료코스 전에 신체검사, 필요에 따라 적절한 방사선 추적검사를 실시한다. 종양진행의 확실한 증거가 있으면 치료를 중단한다.

#### 6. 상호작용

- 1) 이 약은 보조인자이므로 간대사증가로 페노바르비탈, 페니토인, 프리미돈의 혈장농도를 감소시켜 발작가능성이 있는 소아환자의 발작빈도를 증가시킬 수 있으므로, 이 약 고용량과 동시투여 중 또는 투여 후에는 혈장농도를 측정하여 용량을 조절한다.
- 2) 이 약은 5-FU의 효력과 이상반응을 증가시킨다.
- 3) 메토틀렉세이트, 피리메타민 같은 엽산저해 항암제와 동시에 투여하는 경우 항암제의 효력이 감소되거나 완전히 중화된다.

#### 7. 임부 및 수유부에 대한 투여

- 1) 이 약의 사람에 대한 생식연구가 시행된 바 없다. 랫트와 토끼에서 50배의 용량으로 태자독성을 나타내지는 않았으나 동물연구결과로부터 항상 사람에 대해 예측할 수는 없으므로, 임부에게는 유익성이 태아에 대한 위험의 가능성을 상회한다고 판단되는 경우에만 투여한다. 다만 5-FU와 병용시 임부에는 투여하지 않는다.
- 2) 이 약이 모유를 통해서 배설되는지는 알려져 있지 않다. 많은 약물이 모유로 배설되므로 수유부에게 투여하는 경우에는 주의한다. 다만 5-FU와 병용시 수유부에는 투여하지 않는다.

#### 8. 고령자에 대한 투여

- 1) 대장암 환자의 치료에서 5-FU와 병용투여시 고령의 허약환자는 심각한 위장관독성의 위험이 증가될 수 있으므로 특별히 주의한다.
- 2) 일반적으로 고령자는 생리기능이 저하되어 있으므로 주의한다.

#### 9. 적용상의 주의

- 1) 이 약은 경막내 투여하지 않는다.
- 2) 이 약은 칼슘을 포함하고 있으므로 분당 160mg을 초과하지 않도록 주의하여 정맥주사한다.

#### 10. 보관 및 취급상의 주의사항

- 1) 어린이의 손이 닿지 않는 곳에 보관한다.
- 2) 의약품은 원래 용기에서 꺼내어 다른 용기에 보관하는 것은 의약품 오용에 의한 사고 발생이나 품질저하의 원인이 될 수 있으므로 원래의 용기에 넣고 꼭 닫아 보관한다.

#### ■저장방법

밀봉용기, 2℃~8℃에 차광 보관

#### ■포장단위

15mg/2ml × 5 앰플  
50mg/5ml × 1 바이알  
100mg/10ml × 1 바이알  
300mg/30ml × 1 바이알

#### ■제 조 원

15mg/2ml : 바셀버거사, 독일  
(Wasserburger Arzneimittelwerk GmbH,  
Herdestrasse 2, Wasserburg 83512, Germany)

50mg/5ml, 100mg/10ml, 300mg/30ml : 호스피라사, 호주  
(Hospira Australia Pty Ltd,  
1 Lexia Place, Mulgrave, Victoria 3170, Australia)

※사용기한이 경과되었거나 변질·변패·오손된 제품을 구입하였을 때에는 구입한 약국, 도매상, 병·의원을 통하여 즉시 교환해 드립니다.

작성일자 : 2011. 2. 1



수입·판매원

**호스피라코리아 (주)**

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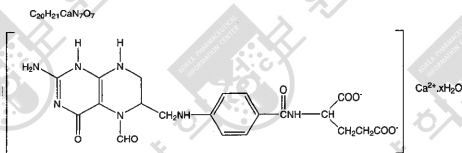
# DBL® Leucovorin Calcium Injection and Tablets



## Name of the Medicine

Calcium folinate

The chemical structure of calcium folinate is shown below, CAS registry number 1492-18-8.



M.W. = 511.5 (Anhydrous)

## Description

DBL® Leucovorin Calcium Injection is a sterile solution of folinic acid (as calcium salt) in water for injections. Sodium chloride is included for isotonicity. Sodium hydroxide or hydrochloric acid is used to adjust pH. Neither the ampoules (3 mg/mL and 15 mg/2 mL) nor the vial presentations (50 mg/5 mL and 300 mg/30 mL) contain a bactericide.

DBL® Leucovorin Calcium Tablets contain calcium folinate equivalent to 15 mg folinic acid.

The following DBL® Leucovorin Calcium Injection presentations: 3 mg/mL, 15 mg/2 mL, 50 mg/5 mL and 300 mg/30 mL contain calcium folinate equivalent to 3 mg, 15 mg, 50 mg and 300 mg folinic acid respectively.

## Pharmacology

### Pharmacological actions

Folinic acid is the formyl derivative of tetrahydrofolic acid which is a metabolite and active form of folic acid. It is effective in the treatment of megaloblastic anaemia caused by folic acid deficiency and is a potent antidote for both the haematopoietic and reticuloendothelial toxic effects of folic acid antagonists, e.g. methotrexate, pyrimethamine, trimethoprim. In some cancers, folinic acid enters and 'rescues' normal cells, in preference to tumor cells, from the toxic effects of folic acid antagonists, due to a difference in membrane transport mechanism. This principle is applied in high-dose methotrexate therapy with 'folinic acid rescue'.

### Pharmacokinetics

Peak plasma levels of folinic acid are reached, on average 40 minutes and 1.7 hours after intramuscular and oral administration, respectively. The bioavailability of an oral dose is almost the same as an equivalent intramuscular dose.

Calcium folinate is rapidly and extensively converted to 5-methyl tetrahydrofolate (an active metabolite) *in vivo*, with less extensive conversion resulting from parenteral, as opposed to oral administration.

Tetrahydrofolic acid and its derivatives are distributed to all body tissues, being concentrated in the liver and found in moderate amounts in the CSF. Following a 15 mg dose given either orally or intramuscularly, peak serum folate concentrations of 0.268 micrograms/mL and 0.241 micrograms/mL were detected. Folinic acid is eliminated mainly as 10-formyl tetrahydrofolate and 5,10-methyl tetra-hydrofolate. The metabolites are mainly excreted via the urine (80-90%), with elimination being logarithmic in doses exceeding 1 mg.

## Indications

Folinic acid has shown good results in the treatment of certain megaloblastic anaemias resulting from folic acid deficiency. This mainly occurs in infants, during pregnancy, in malabsorption syndromes, liver diseases, sprue and malnutrition. It is not more effective than folic acid for these conditions.

Folinic acid has also shown good results in reducing the toxicity and circumventing the effect of folic acid antagonists, if therapeutically desired.

## Contraindications

Folinic acid is improper therapy for pernicious anaemia and other megaloblastic anaemias secondary to the lack of Vitamin B<sub>12</sub>. When treating these conditions with Folinic acid, haematological remission may occur, but neurological manifestations are likely to progress.

## Precautions

Folinic acid should only be used with folic acid antagonists, e.g. methotrexate, or fluoropyrimidines, e.g. 5-fluorouracil, under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb Folinic acid.

Because of the calcium ion content of the Calcium folinate injections, **no more than 160 mg (16 mL)** should be injected intravenously per minute.

Folinic acid may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving folinic acid and fluorouracil. Concomitant granulocytopenia and fever were present in some, but not all, of the patients.

Seizures and/or syncope have been reported rarely in cancer patients receiving folinic acid, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases. Since three patients had recurrent neurological symptoms on rechallenge with folinic acid, further treatment with leucovorin calcium is not recommended in these circumstances.

Simultaneous therapy with a folic acid antagonist and folinic acid is not recommended because the effect of the folic acid antagonist is either reduced or completely inhibited.

Folinic acid has no effect on nonhaematological toxicities of methotrexate, such as the nephrotoxicity resulting from medicine and/or metabolite precipitation in the kidney.

Folinic acid is not suitable for the treatment of pernicious anaemias and other anaemias resulting from lack of vitamin B<sub>12</sub>. Haematological remissions may occur, while the neurological manifestations remain progressive.

## Use in pregnancy (Category A<sup>†</sup>)

### Use in lactation.

It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when folinic acid is administered to a breastfeeding mother.

## Interactions with other medicines

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin and primidone and increase the frequency of seizures in susceptible children.

High oral, intravenous or intramuscular doses of leucovorin calcium may reduce the efficacy of intrathecally administered methotrexate.

Folinic acid may enhance the toxicity of fluorouracil.

**Folinic acid has been reported to be incompatible with droperidol and phosphonosulphate.**

## Adverse Effects

Allergic sensitisation, including anaphylactoid reactions and urticaria, has been reported following both oral and parenteral administration of folic acid. Nausea and vomiting with very high doses of folinic acid have been reported. Seizures and/or syncope have been reported rarely in cancer patients receiving folinic acid, usually in association with fluoropyrimidine administration (see **Precautions**).

## Dosage and Administration

Folinic acid may be given orally, or parenterally by intramuscular injection, intravenous injection or intravenous infusion. Folinic acid should not be administered intrathecally.

### For Hospital Use Only

DBL® Leucovorin Calcium Injection contains no antimicrobial agent. This product is for single use in one patient only.

When required for intravenous infusion, DBL® Leucovorin Calcium Injection may be diluted in 1 litre of 5% w/v glucose in water for injections or normal saline. Such solutions are stable for 24 hours when stored between 2 to 8°C. However, to avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation of the solution. Infusion should be completed within 24 hours and any residue discarded.

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Code 133  
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Oral doses should be taken on an empty stomach or in the fasting state since studies of bioavailability of oral tablets have been done with fasting patients only.

In the treatment of accidental overdosage of folic acid antagonists, e.g. methotrexate, DBL® Leucovorin Calcium should be administered as promptly as possible. As the time interval between antifolate administration and leucovorin calcium rescue increases, DBL® Leucovorin Calcium's effectiveness in counteracting toxicity diminishes.

Monitoring of serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with DBL® Leucovorin Calcium. Delayed methotrexate excretion may be caused by a third space fluid accumulation (ie ascites, pleural effusion), renal insufficiency or inadequate hydration. Under such circumstances, higher doses of DBL® Leucovorin Calcium or prolonged administration may be indicated. Because absorption is saturable, oral administration of doses greater than 25 mg is not recommended. Doses higher than those recommended for oral use must be given intravenously.

**Laboratory tests.** Patients being treated with DBL® Leucovorin Calcium following methotrexate therapy, including inadvertent overdose, or patients with impaired methotrexate elimination, should have serum creatinine and methotrexate levels determined at intervals of 24 hours. Leucovorin Calcium dosage should be adjusted on the basis of laboratory test results.

**DBL® Leucovorin Calcium rescue after methotrexate therapy.** The recommendations for DBL® Leucovorin Calcium rescue are based on a methotrexate dose of 12 to 15 g/m<sup>2</sup> administered by intravenous infusion over four hours (see product information for methotrexate). DBL® Leucovorin Calcium rescue at a dose of 15 mg (approximately 10 mg/m<sup>2</sup>) every six hours for ten doses starts 24 hours after the beginning of the methotrexate infusion. In the presence of gastrointestinal toxicity, nausea or vomiting, DBL® Leucovorin Calcium should be administered parenterally. Serum creatinine and methotrexate levels should be determined at least once daily. DBL® Leucovorin Calcium Injection administration, hydration and urinary alkalinisation (pH of 7.0 or greater) should be continued until the methotrexate level is below  $5 \times 10^{-8}$  M (0.05 micromolar). DBL® Leucovorin Calcium dose should be adjusted or folinic acid rescue extended based on the following guidelines.

| <b>GUIDELINES FOR LEUCOVORIN CALCIUM DOSAGE AND ADMINISTRATION</b>                                                                                                                                   |                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical situation / laboratory findings</b>                                                                                                                                                      | <b>DBL® Leucovorin Calcium Injection dosage and duration</b>                                                                                          |
| <b>Normal methotrexate elimination</b><br>Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours. | 15 mg orally, intramuscularly or intravenously every six hours for 60 hours<br>(ten doses starting at 24 hours after start of methotrexate infusion). |
| <b>Delayed methotrexate elimination</b><br>Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.                      | Continue 15 mg orally, intramuscularly or intravenously every six hours until methotrexate level is less than 0.05 micromolar.                        |

Patients who experience delayed methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate DBL® Leucovorin Calcium therapy, these patients require continuing hydration and urinary alkalinisation and close monitoring of fluid and electrolyte status until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration which are significant but less severe than the abnormalities described above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, DBL® Leucovorin Calcium rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g. medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

**Note.** The above dosage recommendations do not necessarily apply to experimental high dose methotrexate therapy. High dose methotrexate therapy should only be administered by qualified specialists and in hospitals where the necessary facilities are available. Recent published literature should be consulted for details at all times.

**Impaired methotrexate elimination or inadvertent overdosage.**

DBL® Leucovorin Calcium rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion. DBL® Leucovorin Calcium 10 mg/m<sup>2</sup> should be administered intravenously, intramuscular or orally every six hours until the serum methotrexate level is less than 10<sup>-6</sup>M. In the presence of gastrointestinal toxicity, nausea or vomiting, leucovorin calcium should be administered parenterally. Serum creatinine and methotrexate levels should be determined at intervals of 24 hours. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5 x 10<sup>-6</sup> M or the 48 hour level is greater than 9 x 10<sup>-7</sup> M, the dose of leucovorin calcium should be increased to 100 mg/m<sup>2</sup> intravenously every three hours until the methotrexate level is less than 10<sup>-6</sup>M.

Hydration (3 L/day) and urinary alkalinisation with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

**Treatment of megaloblastic anaemias. Parenteral administration.** Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

**Oral administration.** Daily doses of 5 to 15 mg.

**Treatment of pyrimethamine overdosage.** The dosage of pyrimethamine in treating toxoplasmosis is 10 to 20 times its dosage for malaria and approaches the toxic level. Since DBL® Leucovorin Calcium is not utilised by protozoa, it can be given simultaneously without impairing the effectiveness of therapy. The usual dosage is 3 to 9 mg/day by intramuscular injection for three days or until the platelet and leucocyte counts have reached safe levels.

## **Overdosage**

Excessive amounts of folic acid nullify the chemotherapeutic effect of folic acid antagonists.

In case of overdose, immediately contact the Poisons Information Centre for advice (In Australia, call 13 11 26, in New Zealand, call 0800 764 766).

## **Storage and Presentation**

*Injection* Store at 2 to 8°C. (Refrigerate. Do not freeze). Protect from light.

*Tablets.* Store below 30°C.

DBL® Leucovorin Calcium Injection 3 mg/1 mL ampoule (5 ampoules per pack)

DBL® Leucovorin Calcium Injection 15 mg/2 mL ampoule (5 ampoules per pack)

DBL® Leucovorin Calcium Injection 50 mg/5 mL vial (single vial per pack)

DBL® Leucovorin Calcium Injection 300 mg/30 mL vial (single vial per pack)

DBL® Leucovorin Calcium Tablets 15 mg (10 tablet pack)

## **Poison Schedule of the Medicine**

Schedule 4

## **Name and Address of Sponsor**

### Australian Sponsor

Hospira Australia Pty Ltd

ABN 58 097 064 330

Level 3

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Melbourne VIC 3004

Australia

### New Zealand Sponsor

Hospira NZ Limited

23 Haining Street

Te Aro

Wellington

New Zealand

Date of TGA approval: 22 May 2008

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† *Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without proven increase in frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.*