

本藥限由醫師使用受

## 特慕血舒靜脈輸注液 10% Tetraspan 10% solution for infusion

**成分** 每1000 ml包含:

主成分: Poly(O-2-hydroxyethyl) starch (HES)

100.0 g

(莫耳置換比: 0.42) (平均分子量: 130,000 Da) Sodium chloride

Potassium chloride Calcium chloride dihydrate Magnesium chloride hexahydrate

Sodium acetate trihydrate

Malic acid

電解值濃度:

Sodium Potassium Calcium Magnesium

Chloride Acetate Malate

pH: Theoretical osmolarity渗透壓理論值:

Acid titre:

賦形劑: Sodium hydroxide (調節酸鹼值) 和輸注用水

劑型

静脈輸注液

澄清、透明、無色且無雜質之水溶液

血漿代用品與血漿蛋白, ATC 碼:BO5A AO7。

適應症

預防及治療低血容積低下及休克。

每日劑量與輸注速率必須按照病患的失血量、血液動力學參數之維持或恢 復情形來決定。

最初的10-20毫升應以緩慢速率輸注,並嚴密觀察病患的反應,以便儘早 發現可能出現之過敏反應。

福岡市 最高輸注速率應視臨床需求而定。急性休克病患之輸注速率最高可為20毫升/公斤體重/小時 (相當於0.33毫升/公斤/分鐘或2.0公克hydroxyethyl starch/ 公斤體重/小時)。

生命受到威脅時,可以手動加壓輸注500毫升。請參見下述「輸注方式與 治療時間」

每日最高輸注劑量: Tetraspan 10% 每日最高輸注劑量為30毫升/公斤體重 (相當於3.0公克 hydroxyethyl starch/公斤體重)。以70公斤病患而言,相等於輸注2000毫升 Tetraspan 10%

目前並無Tetraspan10% 用於兒童的治療經驗,只有在評估對兒童本身的助益高於危險時,才能給予兒童Tetraspan 10%,且需特別小心監控。

輸注方式與治療時間:

静脈輸注方式給予。

若欲利用加壓方式達到快速輸注,輸注前必須將所有空氣自塑膠包裝及輸 液管路中排空,以防止輸注時之空氣栓塞。

治療期長短應視血容積減少 (hypovolemia) 之時間與程度、輸注治療時對血 液動力的影響 (hemodynamic effects),和血液稀釋情況而定。

禁忌症

- 體液蓄積的情形,包括肺水腫 腎衰竭合併少尿或無尿
- 顱內出血
- 高血鉀症
- 嚴重高血鈉症或高血氣症
- 對hydroxyethyl starch或其他賦型劑過敏
- 肝功能嚴重受損
- 心臟衰竭

使用時特別警告事項與注意事項 應避免因用藥過量而導致體積超載的情形,尤其對於心臟功能不全病患應

對於腎功能障礙病患,應特別照護並選擇適合劑量。 對於高血容積之年長患者,應特別徹底監控並選擇適合劑量,以降低腎功

對於高血谷模之中表思者,應特別做底監控並無達過音劑量,以降低質功能受損的風險。 定期監控血清電解值、輸液平衡與腎功能,並確保病患攝取足夠水分。 若病患出現嚴重脱水情形,第一時間應給予靜脈電解值溶液。 若病患有肝功能異常和血液凝固障礙,如血友病和温韋伯氏病(v. Willebrand's disease),則需給予特別照護。 輸注Tetraspan10%前,應先驗血以確保血型正確。 因為有過敏反應發生可能性,故應密切監控病患,並以低流速輸注(請參目副作用)。

輸注HES後,血清澱粉酵素濃度會暫時升高,故不適合作胰臟功能診斷

孕婦及哺乳婦

目前並無孕婦使用Tetraspan 10% 的相關臨床資料。以低分子量與低莫耳 置換比之代用HES進行動物試驗顯示,只有在對孕婦本身的助益高於對胎 兒的潛在危險時,才會給予孕婦Tetraspan 10%。

目前並不知道Tetraspan 10% 會不會通過乳汁分泌,使用於哺乳婦時須特 別注意。

與其他藥物的交互作用 目前仍未發現Tetraspan 10% 與其他藥物或營養產品之間有產生交互作用 之可能。由於缺乏相關研究,使用此藥物時,應避免與他種藥物混合使

與會引起鉀或鈉離子滯留的藥物併用時,需特別謹慎。鈣離子濃度上升可 能會增加醣心配糖體毒性作用之危險性。

不良反應依其發生頻率分成下列等級下述標準定義:

非常常見 (>1/10)、常見 (>1/100、<1/10) 、少見 (>1/1000、<1/100) 、罕見 (>1/10000、<1/1000)

最常被報導的不良反應大多直接與澱粉溶液輸注治療和劑量給予有關, 例如因沒有同時補充血液組成成分的血管內容量擴張造成血液稀釋作 用。也可能發生凝血因子被稀釋。 過敏反應相當罕見且與給予劑量多寡無關。

血液與淋巴系統異常

血球容積比下降且血漿蛋白濃度降低導致血液稀釋。 常見(依使用劑量而定):

免疫系統異常

罕見:

6.25 g

0.30 g

0.37 g

0.20 g

3.27 g

0.67 g

140 mmol/l

4.0 mmol/l

2.5 mmol/l

1.0 mmol/l

118 mmol/l

24 mmol/l

5.0 mmol/l

< 2.0 mmol/l

5.6-6.4 296 mOsmol/l 一元 各種過敏反應,請見下述*「過敏反應」*。

·般異常與輸注部位症狀

重複輸注HES多天,尤其是達到高累積劑量時,通常會導致難以治療的搔癢症(發癢)。此搔癢症可能在停止輸注數週後發生且可能會持續數月。Tetraspan 是否可能會引起此種不良反應尚未被充分的研究。

研究調查

非常常見:

輸注hydroxyethyl starch時,血清 α-澱粉酵素濃度會升高,係因hydroxyethyl starch引起澱粉酵素複合物 (amylase complex) 以及腎臟和腎臟外排除延遲的結果,不應誤解為胰臟疾病之診斷。

不同強度的過敏反應可能發生於輸注hydroxyethyl starch後,所有病患輸注 時,應嚴密監控其過敏反應,一旦出現過敏反應,應立即停止輸注並施

以適當的緊急醫療處置。 並無任何的檢測可以事先診斷出病患可能會有過敏反應,也無法預料病 患過敏反應的結果和嚴重度。 使用類固醇 (corticosteroid) 的預防治療未被證實有效。

備註: 如果有任何説明書中未列出的副作用發生,請告知醫師或藥師。

為性用藥過量最大的危險在於導致體內循環系統血容積增加。發生用藥 過量時,應立即停止輸注並給予利尿劑治療,以緩解上述情形。

Tetraspan 10% 為一種膠體狀的血漿代用品,含 10% hydroxyethyl starch (HES) 溶於電解值平衡溶液中,其平均分子量為 130,000 Da,莫耳置換比 為 0.42。

Tetraspan 10% 高於血管內膠質壓力/高脹壓 (hyperoncotic),例如,在血管

內增加的血漿體積高於輸入的體積。 體積影響的持續時期主要決定於莫耳置換比和較小的平均分子量。HES聚合物在血管內的水解作用可導致持續性的釋出較小的分子,此些小分子在經由腎臟排除前可有效維持血管內膠質壓力。

Tetraspan 10% 可能會降低血容積比 (haematocrit) 和血漿黏度。

Tetraspan 10% 可能實際低血各類化 (flaerinatocrit) 和血聚黏度。 若同體積投藥,體積擴張的作用可維持至少6小時。 Tetraspan 10% 中的陽離子是以人體生理血漿電解質濃度為依據;陰離子是結合了氣、醋酸鹽和蘋果酸,目的是將發生低氣血症 (hyperchloraemia) 和酸中毒 (acidosis) 的風險降到最低。以醋酸鹽和蘋果酸取代乳酸鹽,其目的是用來降低發生乳酸中毒的風險。

Hydroxyethyl starch 是由各種不同分子量和取代度 (degree of substitution) 的分子組成的混合物,其排除取決於分子量和取代度。分子小於所謂的腎閾值 (renal threshold) 可被腎絲球過濾 (glomerular filtration) 排除;大分子可被α-澱粉酵素降解 (α-amylase),之後再由腎臟排除。降解速率會隨著 取代度增加而降低,約50% 給予的劑量在24小時內會排泄至尿液。 在單一輸注1000 ml Tetraspan 6% 後,血漿清除率 (plasma clearance) 為 19 ml/min 且血清最終半衰期 (terminal serum half-life) 約為 12 小時。

臨床前研究之安全資訊

Tetraspan 10% 並無執行動物毒理試驗。已發表的動物毒性研究,以小分 Tetraspan 10% 亚無訊行動物毒理試驗。已餐表的動物毒性研究,以小分子HES產品重複做高容積治療,顯示在不同的器官中有出血和組織細胞增生 (histiocytesis: 泡沫狀組織球 (histiocytes)/巨噬細胞累積) 現象,並伴隨有肝、腎和脾臟重量增加。亦有報告指出不但有脂肪浸潤 (fat infiltration)和器官形成空泡 (vacuolation of organs) 而且血漿之天門東氨酸轉胺酵素 (AST) 和丙氨酸轉胺酵素 (ALT) 亦會提高。部分的影響可能起因於血液稀釋、輸血相關之循環也載和澱粉吸收並累積在吞噬細胞。

釋、糊血相關之值壞起氧和概念物及收立系積在谷盛細胞。 相類似的HES產品已被報導在標準測試下並無基因毒性。 HES產品的生殖毒性研究顯示陰道出血、胚胎胎兒毒性和畸形等病兆奧重 複對試驗動物給藥有關連,這些影響可能與血液稀釋並導致胎兒缺氧和 血容量過多相關。出血症狀可能部份與HES直接影響血液凝固相關。在治 療血容量過低之病患應該避免因輸血相關之循環超載造成血液稀釋

超過標籤上所標示之保存期限時,請勿再使用。

貯存/使用/攜帶

不可冷凍。 25℃以下储存。

限單次使用。一旦打開後必須立即使用,如有未用完的溶液,應兼置勿

只有在溶液澄清透明、未發現顆粒且包裝完整時才可使用。

版次

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Ecoflac plus塑膠容器加壓輸注説明:

若欲利用加壓方式達到快速輸注,輸注前必須將所有空氣自塑膠包裝及 輸液管路中排除,以防止輸注時之空氣栓塞。

為排除聚乙稀Ecoflac plus塑膠容器內之空氣,則可使用輸液套或過濾針

#### tcoffac plus型膠軟瓶架作記明

#### 1. 重力輸注

- 接上輸注管路,使液體填充滴定室之一半,使液體 充满管路並避免產生氣泡
- 關閉輸注管路的空氣閥
- 將輸注管路接到留置針 - 打開流速控制器,開始輸注



- 4.加墜糊注 接上輸注管路
- - 將容器朝上放置 - 打開管夾,將容器管路中的空氣排空,併使液體充填
  - 滴定室之一半 - 將容器轉向,排空管路中的空氣
  - 關閉管夾
  - 放置加壓氣囊
  - 加壓
  - 打開流速控制器,開始輸注





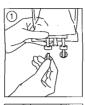
#### Ecobag塑膠軟袋操作説明

#### 1. 容器準備

- 檢查容器並確保包裝無損毀
- 檢查溶液並確保溶液澄清透明且無變色 以扭轉方式打開容器之封口,開啟的輸注口
- 為無菌。
- (曲 ⇒ 輸注口) (働 ⇨ 加藥口)

#### 2. 重力輸注

- 關閉輸注管路的空氣閥及流速控制器
- 接上輸注管路
- 使液體填充滴定室之一半 - 使液體充滿管路並避免產生氣泡



- 將輸注管路接到留置針
- 打開流速控制器,開始輸注





#### 5.加壓輸注

- 接上輸注管路
- 將容器朝上放置
- 打開管夾,將容器管路中的空氣排空,併使液體充填 滴定室之一半
- 將容器轉向,排空管路中的空氣
- 關閉管夾



- 放置加壓氣囊
- 加壓
- 打開流速控制器,開始輸注





## Tetraspan 10% 有下列的包裝及容量

塑膠軟瓶 (Ecoflac plus):

10 x 500 毫升

塑膠軟袋 (Ecobag):

10 x 250毫升 20 x 250毫升

10 x 500毫升

20 x 500毫升 10 x 1000毫升 製浩廠

B. Braun Medical AG Route de Sorge 9

CH-1023 Crissier, Switzerland

## 國外許可證持有者

B. Braun Melsungen AG 34209 Melsungen, Germany

### 藥商

台灣柏朗股份有限公司 台北市中山區南京東路三段132號11樓





## **Directions for Use**

B. Braun Melsungen AG, 34209 Melsungen, Germany

# **Tetraspan 10% solution for infusion**

Composition 1000 ml contains

Active substances: Poly(0-2-hydroxyethyl) starch (HES) (Molar substitution: 0.42)

(Average molecular weight: 130,000 dalton) Sodium chloride 6.25 q Potassium chloride 0.30 g Calcium chloride dihydrate 0.37 g Magnesium chloride hexahydrate 0.20 g 3.27 g 0.67 g Sodium acetate trihydrate Malic acid

Electrolyte concentration: Sodium

Potassium 4.0 mmol/l Calcium 2.5 mmol/l Magnesium 1.0 mmol/l Chloride Acetate 118 mmol/l 24 mmol/l Malate 5.0 mmol/l 5.6-6.4 Theoretical osmolarity: 297 mOsmol/l

Acid titre: Excipients:

Sodium hydroxide (for pH adjustment), Water for Injections

#### Pharmaceutical form

Solution for infusion.

Pharmaco-therapeutic group

Blood substitutes and plasma protein fractions, ATC code B05A A07

Treatment of imminent or manifest hypovolaemia and shock.

The daily dose and infusion rate depend on the extent of blood loss and how much fluid is required to maintain or restore haemodynamic parameters.

The initial 10-20 ml should be infused slowly and under careful monitoring of the patient so that any anaphylactoid reaction can be detected as soon as possible.

Maximum infusion rate:

The maximum infusion rate depends on the clinical situation. Patients in acute shock may be administered up to 20 ml/kg body weight per hour (equivalent to 0.33 ml/kg/min or 2.0 g hydroxyethyl starch/kg body weight per hour). In life-threatening situations, 500 ml may be administered rapidly by manual pressure infusion. See also "Method of administration and duration of therapy."

Maximum daily dose:

Up to 30 ml Tetraspan 10 % /kg body weight (equivalent to 3.0 g hydroxyethyl starch/kg body weight). This is equivalent to 2000 ml Tetraspan 10 % for a 70 kg patient.

There is no experience from treatment of children with Tetraspan 10 %.

Therefore Tetraspan 10 % should only be given to children after careful benefit/risk assessment and then only with particular caution.

Method of administration and duration of therapy:

For intravenous infusion.

In case of a rapid infusion under pressure, all air must be withdrawn from the plastic container and infusion set prior to infusion. This is to avoid the risk of a possible air embolism associated with the infusion.

The duration of therapy depends on the duration and extent of hypovolaemia, the haemodynamic effects of the administered treatment and the level of haemodilution.

## Contraindications

- Hyperhydration states including pulmonary edema.
- Renal failure with oliguria or anuria.
- Intracranial bleeding.
- Severe hypernatremia or severe hyperchloremia.
- Hypersensitivity to hydroxyethyl starch or to any of the excipients.
- Severely impaired hepatic function. Congestive cardiac failure.

Special warnings and precautions for use Volume overload from overdosage should always be avoided. Dosage should be carefully adjusted, especially in patients with cardiac insufficiency.

Particular caution should be exercised in patients with renal impairment. The dose may need to be adjusted.

Elderly patients with hypervolaemia should be thoroughly monitored, and the

dosage should be adapted, in order to avoid impairment of renal function.

Serum electrolytes, fluid balance, and kidney function should be monitored.

Adequate fluid intake must be ensured. Patients with severe dehydration should first receive intravenous electrolyte

Particular caution should be exercised in patients with hepatic insufficiency and

in those with blood coagulation disorders particularly haemophilia and known or suspected v. Willebrand's disease. To ensure correct blood typing, a blood sample should be taken prior to the

administration of Tetraspan 10 %. Because of the possibility of allergic (anaphylactic/anaphylactoïd) reactions, appropriate monitoring of patients is necessary, and a slow infusion rate should be initiated (See section **Undesirable effects**).

Elevated serum alpha-amylase concentrations may be observed temporarily following administration of HES solutions and must not be considered diagnostic of impaired pancreatic function (See section Undesirable effects).

Pregnancy and lactation

No animal toxicology studies with Tetraspan 10 % have been conducted. Animal studies with low molecular weight and low substituted HES show that Tetraspan 10 % should be used during pregnancy only if the potential benefits outweigh the possible risk to the foetus.

As it is not known whether the modified starch in Tetraspan 10 % is excreted in breast milk, caution should be exercised when administered to lactating women.

No interactions with other drugs or nutritional products are known to date. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## Undesirable effects

Adverse reactions have been ranked under headings of frequency using the following convention:

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000)

The most commonly reported adverse reactions are directly related to the therapeutic effects of starch solutions and the doses administered, *i.e.*, hemodilution resulting from expansion of the intravascular space without concurrent administration of blood components. Dilution of coagulation factors may also occur.

Hypersensitivity reactions, which are very rare, are not dose-dependent.

Blood and lymphatic system disorders

Very common:

Reduced hematocrit and decreased plasma protein concentrations as a result of hemodilution.

Higher doses of hydroxyethyl starch cause dilution of coagulation factors and may thus affect blood clotting. Bleeding time and aPTT may be increased and FVIII/vWF complex levels may be reduced after administration of high doses. See "Special warnings and special precautions for use".

Immune system disorders

100.0 g

140 mmol/l

< 2.0 mmol/l

Anaphylactic reactions of various intensities. For details see "Anaphylactic reactions" below.

General disorders and administration site conditions

Uncommon:

Repeated infusions of HES for many days, especially when high cumulative doses are reached, usually lead to pruritus (itching) which responds very poorly to therapy. This pruritus may occur many weeks after discontinuing the starch infusions and may persist for months. The likelihood of this adverse effect has not been adequately studied for Tetraspan.

Investigations

Very common:

The infusion of hydroxyethyl starch produces elevated serum  $\alpha$ -amylase concentrations. This effect is the result of the formation of an amylase complex of hydroxyethyl starch with delayed renal and extrarenal elimination. It should not be misinterpreted as evidence of a pancreatic disorder.

Anaphylactic reactions

Anaphylactic reactions of various intensities may occur after administration of hydroxyethyl starch. All patients receiving starch infusions should therefore be closely monitored for anaphylactic reactions. In case of an anaphylactic reaction, the infusion must be stopped immediately and the usual emergency treatment instituted.

There are no tests to identify patients in whom an anaphylactic reaction is likely, nor can the outcome and severity of such a reaction in a given patient be predicted. The prophylactic use of corticosteroids has not proved effective.

Patients should inform their doctor or pharmacist if they notice any side effect not mentioned in this leaflet.

The greatest risk associated with an acute overdose is hypervolemia. In this case, the infusion must be stopped immediately, and administration of diuretics be

Pharmacodynamic properties

Tetraspan 10% is a colloidal plasma volume substitute containing 100 mg/ml hydroxyethyl starch (HES) in a balanced electrolyte solution. The mean molecular weight is 130,000 Daltons and its molar substitution is 0.42.

Tetraspan 10% is hyperoncotic, i.e. the increase in the intravascular plasma volume exceeds the infused volume.

The duration of the volume effect is primarily based on molar substitution and to a lesser extent on the mean molecular weight. Intravascular hydrolysis of HES polymers results in a continuous release of smaller molecules which in turn are

oncotically active before they are excreted via the kidneys. Tetraspan 10% may lower haematocrit and plasma viscosity.

With isovolaemic administration, the volume expanding effect is maintained for at least 6 hours.

The cation pattern in the crystalloid component Tetraspan 10% is adapted to physiological plasma electrolyte concentrations. The anion pattern is a combination of chloride, acetate and malate, the purpose of which is to minimise the risk of hyperchloraemia and acidosis. Addition of acetate and malate instead of lactate anions are intended to reduce the risks of lactic acidosis.

Pharmacokinetic properties

Hydroxyethyl starch is a mixture of several various molecules with a different molecular weight and degree of substitution. Elimination is dependent on molecular weight and degree of substitution. Molecules smaller than the socalled renal threshold are eliminated by glomerular filtration. Larger molecules are degraded by alpha-amylase and are thereafter eliminated renally. The rate of degradation decreases with increased degree of substitution. Approximately 50% of the administered dose is excreted into urine within 24 hours.

After a single infusion of 1000 ml Tetraspan 60 mg/ml, plasma clearance is 19 ml/

min and the terminal serum half-life is about 12 hours.

Preclinical safety data

No toxicological animal studies have been conducted with Tetraspan 10%. Published animal toxicological studies of repeated hypervolaemic treatment with similar HES products have revealed bleeding and extensive histiocytosis (accumulation of foamy histiocytes/macrophages) in several organs with an increase in weight of the liver, kidneys and spleen. Infiltration of fat and vacuolation of organs as well as elevations of plasma AST and ALT have been reported. It has been suggested that some of the effects described were caused by haemodilution, circulatory overload and uptake and accumulation of starch in phagocytic cells.

Similar HES products have been reported to be non-genotoxic in standard tests. Reproductive toxicity studies of HES products showed vaginal bleeding and signs of embryo-/foetotoxicity and teratogenicity associated with repeated administration to laboratory animals. These effects may be related to haemodilution and result in foetal hypoxia and hypervolaemia. Bleeding may partly also be related to direct effects of HES on blood coagulation. Haemodilution due to circulatory overload should always be avoided when treating hypovolaemic patients.

**Expiry date** 

The product must not be used beyond the expiry date stated on the labelling.

## Instructions for storage / use / handling

Do not freeze.

Do not store above 25°C

For single use only. Use immediately after first opening and discard any unused Use only clear solution, practically free from particles, from intact containers.

Date of last revision: 07.2007

## Further information

Pressure infusion from Ecoflac plus plastic containers:

If wished to administer by rapid infusion under pressure, all air must be withdrawn from the plastic container and infusion set prior to infusion.

To expel air from the polyethlene container Ecoflac plus a vented giving set or a filtered venting needle should be used.

### Instructions for Handling the Ecoflac plus Container

#### 1. Gravity infusion

- Insert infusion set, fill half of drip chamber, fill infusion tube avoiding bubbles.
- Close air vent of infusion set.
- Connect infusion tube to cannula/catheter.
- Open clamp and start infusion wit air vent closed



#### 2. Pressure infusion

- Insert infusion set.
- Hold container upright.
- Leave clamp open, expel air from container and fill half of drip chamber. - Turn container and expel air from infusion device.
- Close clamp.
- Place container in pressure cuff.
- Build up pressure.
- Open clamp and start infusion.





## Instructions for Handling the Ecobag Container

#### 1. Preparation of the container

- Check container and closure are intact.
- Check contents for clarity and discoloration
- Open container by twisting off the corresponding toggle. The opened infusion port site is sterile.
- ( Additive port)

#### 2. Gravity infusion

- Close air vent and roller clamp of infusion set.
- Insert infusion set.



- Fill half of drip chamber.
- Fill infusion tube avoiding bubbles.



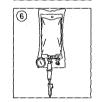
- Connect infusion tube to cannula/catheter.
- Start infusion, leaving air vent closed.





## 5. Pressure infusion

- Insert infusion set.
- Hold container upright. - Leave roller clamp open, expel air from container and fill
- half of drip chamber.
- Turn container and expel air from infusion set.
- Close roller clamp.
- Place container in pressure cuff.
- Build up pressure.
- Open roller clamp and start infusion.



## Tetraspan 10% is available in the following types of packaging and contents:

Polythene plastic bottle (Ecoflac plus) 10 x 500 ml

Plastic bags (Ecobag)

10 x 250 ml

20 x 250 ml 10 x 500 ml

20 x 500 ml

10 x 1000 ml





