"TBSF" Human Immunoglobulin for Intravenous Use

Taiwan

NAME OF THE MEDICINE
Human Normal Immunoglobulin solution for intravenous injection.

DESCRIPTION
"TBSF" Human Immunoglobulin for Intravenous Use is prepared in cooperation with the "Self sufficiency" recommendation set forth by the Taiwan Department of Health, from pooled human plasma obtained from voluntary donors.
"TBSF" Human Immunoglobulin for Intravenous Use is a sterile, preservative free solution containing 6 g of human protein and 10 g of maltose in each 100 mL. The solution has a pH of 4.25. Isotonicity is achieved by the addition of maltose. At least 98% of the protein has the electrophoretic mobility of immunoglobulin G (IgG). At least 90% of the protein is IgG monomer and dimer. Based on three preclinical and four clinical batches, the distribution of IgG subclasses present in "TBSF" Human Immunoglobulin for Intravenous Use is, on the average, 61% IgG_1, 36% IgG_2, 3% IgG_3 and 1% IgG_4. "TBSF" Human Immunoglobulin for Intravenous Use contains only trace amounts of Immunoglobulin A (IgA) (nominally < 0.025 mg/mL). "TBSF" Human Immunoglobulin for Intravenous Use is intended for intravenous administration.
"TBSF" Human Immunoglobulin for Intravenous Use is made by chromatographic fractionation of large pools of human plasma obtained from voluntary donors. The protein has not been chemically or enzymatically modified. The manufacturing process contains specific steps to reduce the possibility of virus transmission including pasteurisation (heating at 60°C for 10 hours) and incubation at low pH.

SPECIAL WARNING
This product is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain virus markers. In addition, virus removal and inactivation procedures are included in the manufacturing process. Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products. Hence, if patients are infected after using this product, it must be reported to the medical practitioner, the distributor or the manufacturer. Please discuss the risks and benefits of this product with your medical practitioner.
The current procedures applied in the manufacture of this product are effective against enveloped viruses such as HIV (human immunodeficiency virus), hepatitis B and hepatitis C viruses, and the non-enveloped virus, hepatitis A. These procedures may be of limited value against the non-enveloped virus, parvovirus B19. However, the product contains specific antibodies directed against parvovirus B19.
Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

The clinical trials for "TBSF" Human Immunoglobulin for Intravenous Use are based on Intragam®P, the comparable purified human immunoglobulin for intravenous use (IVIG) manufactured by CSL Limited for distribution in Australia.

PHARMACOLOGY AND PHARMACOKINETICS
The steady-state kinetic parameters for serum IgG were determined in 11 patients (9 male, age 28-76 years) with primary immunodeficiency disorders, following the administration of monthly intravenous infusions of Intragam®P for six months. The dose of Intragam®P was individualised in the range 0.35 to 0.53 g/kg. The mean serum IgG concentration ranged from a trough of 7.4±1.1 g/L to a peak of 15.8±1.7 g/L, the mean clearance was 4.1±0.8 mL/h and the mean half-life 39.7±7.8 days. Mean recovery, the increase in serum IgG concentration as a percentage of the expected concentration after an Intragam®P infusion, was 44.0±2.0% (see **CLINICAL TRIALS**).

CLINICAL TRIALS

Primary Immune Deficiency

The efficacy of Intragam®P was assessed in 35 patients (age 6-76 years; 21 male) with primary immune deficiency disorders, following the administration of monthly intravenous infusions of Intragam®P for six months. The dose of Intragam®P was individualised in the range 0.2 to 0.67 g/kg. The mean number of days of hospitalisation over the 6 month period was 2.8±9.0 and the mean number of days absent from work or school due to illness, 5.3±6.4. These figures were similar to historical data relating to other intravenous immunoglobulins.

Idiopathic Thrombocytopenic Purpura (ITP)

The efficacy of Intragam®P was assessed in 17 patients (age 21-72 years; 5 male) with ITP (6 acute, 11 chronic), following intravenous infusion of Intragam®P once daily for 1-3 consecutive days. The dose of Intragam®P was individualised up to a maximum total cumulative dose of 2 g/kg bodyweight. Following administration of Intragam®P, a total of 13 patients (76.5%) achieved platelet count responses which were good ($50x10^9$/L-$150x10^9$/L) or excellent (>$150\ x10^9$/L). Platelet counts were maintained at ≥$50\ x10^9$/L for up to 35 days with a median of 17.24 days (95% CI 10.35, 24.12). These figures were similar to historical data relating to other intravenous immunoglobulins.

Adverse events encountered during both clinical trials are outlined in **ADVERSE EFFECTS**.

INDICATIONS

"TBSF" Human Immunoglobulin for Intravenous Use is indicated for replacement IgG therapy in:

- primary immunodeficiency;
- myeloma and chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections;
- congenital or acquired immune deficiency syndrome with recurrent infections.

"TBSF" Human Immunoglobulin for Intravenous Use is indicated for immunomodulatory therapy in:

- Idiopathic Thrombocytopenic Purpura (ITP), in adults or children at high risk of bleeding or prior to surgery to correct the platelet count;
- allogeneic bone marrow transplantation;
- Kawasaki disease.

Comprehensive evidence-based guidelines describing appropriate clinical use of intravenous immunoglobulin in ITP have been published and should be followed wherever possible to avoid the inappropriate utilisation of this blood product [1,2].

CONTRAINDICATIONS

"TBSF" Human Immunoglobulin for Intravenous Use is contraindicated in patients who have had a true anaphylactic reaction to a human immunoglobulin preparation.

PRECAUTIONS

"TBSF" Human Immunoglobulin for Intravenous Use should only be administered intravenously. Other routes of administration have not been evaluated. It is possible that "TBSF" Human Immunoglobulin for Intravenous Use may, on rare occasions, cause a precipitous fall in blood pressure and a clinical picture of anaphylaxis. Therefore, adrenaline and oxygen should be available for the treatment of such an acute reaction.

"TBSF" Human Immunoglobulin for Intravenous Use contains trace amounts of IgA which may provoke anaphylaxis in patients with IgA antibodies, such as those with selective IgA deficiency.

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IVIG treatment. The syndrome usually begins within several hours to two days following IVIG treatment. It is characterised by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye

movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis, predominantly from the granulocytic series, and elevated protein levels. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IVIG treatment. Discontinuation of IVIG treatment has resulted in remission of AMS within several days without sequelae.

There have been occasional reports of renal dysfunction and acute renal failure in patients receiving IVIG products. Patients at increased risk are those with pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis and paraproteinaemia, and those taking concomitant nephrotoxic drugs. The majority of such incidents have been associated with sucrose-containing products. Whilst there is no sucrose in "TBSF" Human Immunoglobulin for Intravenous Use, the following precautions should be followed: Patients should be adequately hydrated prior to the initiation of the IVIG infusion and the recommended dose should not be exceeded. Renal function should be monitored in patients at increased risk of developing acute renal failure. If renal function deteriorates, discontinuation of IVIG should be considered.

Positive direct antiglobulin tests and red cell haemolysis have been reported following high dose infusion of intravenous immunoglobulin due to the presence of anti-A, anti-B, and occasionally anti-D or other erythrocyte antibodies in the product. Such red cell sensitisation may cause crossmatching difficulties and transient haemolytic anaemia.

Patients of blood group A or AB receiving high dose IVIG (>0.4 g/kg every 4 weeks) especially those with reduced bone marrow reserve or post haemopoietic stem cell transplantation appear to be more susceptible.

Patients receiving high dose IVIG (>0.4 g/kg every 4 weeks) should have a pre-infusion ABO blood group determined and have their haemoglobin monitored in the days following therapy for evidence of clinically significant haemolysis.

Thrombotic events have been reported in association with IVIG therapy. Risk factors include advanced age, immobility, impaired cardiac output, and conditions associated with increased plasma viscosity, such as hypertriglyceridaemia and monoclonal gammopathies.

In patients with a normal acid-base compensatory mechanism, the acid load delivered by the largest dose of the preparation would be neutralised by the buffering capacity of whole blood alone, even if the dose were to be infused instantaneously. In patients with limited or compromised acid-base compensatory mechanisms including neonates, consideration should be given to the effect of the additional acid load that the preparation might present.

Prolonged administration (over 6 hours) using large doses (greater than 0.4 g/kg) may result in thrombophlebitis at the infusion site.

Patients who receive IVIG:
- for the first time,
- when there has been a long interval since the previous infusion or,
- in rare cases, when the human normal immunoglobulin product is switched,

may experience a higher frequency of adverse events, including those of a minor nature.

Reactions to IVIG tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. It is recommended that the patient's vital signs and general status are monitored regularly throughout the infusion.

Mutagenicity, Carcinogenicity and Impairment of Fertility
No mutagenicity, carcinogenicity or reproductive toxicity studies have been conducted with "TBSF" Human Immunoglobulin for Intravenous Use. There have been no reports of such effects associated with the use of CSL's plasma derived products.

Use during Pregnancy and Lactation
The safety of this medicinal product for use in human pregnancy and lactation has not been established in controlled clinical trials. "TBSF" Human Immunoglobulin for Intravenous Use should therefore only be given with caution to pregnant women and breast feeding mothers. Immunoglobulins are excreted in breast milk. Clinical experience

with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Interactions with other medicines
The interaction of "TBSF" Human Immunoglobulin for Intravenous Use with other drugs has not been established in appropriate studies.

Passively acquired antibody can interfere with the response to live, attenuated vaccines. Therefore, administration of such vaccines, e.g. poliomyelitis or measles, should be deferred until approximately three months after passive immunisation. By the same token, immunoglobulins should not be administered for at least two weeks after a vaccine has been given.

Interference with glucose estimations
The maltose present in "TBSF" Human Immunoglobulin for Intravenous Use may interfere with some blood glucose measurements, resulting in the overestimation of blood glucose results. If this glucose measurement is used to guide treatment, hypoglycaemia may occur. Only certain glucose tests using glucose dehydrogenase have been implicated, so when monitoring glucose levels in patients receiving "TBSF" Human Immunoglobulin for Intravenous Use, information from the manufacturer of the glucose meter and/or test strips, should be reviewed to ensure that maltose does not interfere with the blood glucose reading.

ADVERSE EFFECTS
Patients naïve to immunoglobulin may experience a higher frequency of adverse events, including those of a minor nature. Reactions to intravenous immunoglobulin tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. It is recommended that the patient's vital signs and general status are monitored regularly throughout the infusion.

Reactions Associated with Intragam®P in Clinical Trials
Primary Immune Deficiency
The following adverse reactions occurred in 35 patients receiving Intragam®P during the clinical trial (expressed as the number of patients experiencing the adverse reaction): headache (8), migraine (2), anaemia (2), nausea (2), vertigo (1), neutropenia (1), thrombocytopenia (1) and fatigue (1). The dose of Intragam®P ranged from 0.2 to 0.67 g per kg bodyweight per month.

Idiopathic Thrombocytopenic Purpura (ITP)
The following adverse reactions occurred in 17 patients receiving Intragam®P during the clinical trial (expressed as the number of patients experiencing the adverse reaction): headache (10), positive direct Coombs test (5), haemolysis (4), nausea (3), rigors (3), fever (2), myalgia (1), somnolence (1), abdominal pain (1), vomiting (1), hypertension (1), flushing (1), haemolytic anaemia (1), leucopenia (1), reticulocytosis (1), lymphopenia (1), allergic reaction (1), hot flushes (1) and injection site inflammation (1). The dose of Intragam®P ranged from 0.66 to 2 g per kg bodyweight received via infusion once daily over 1-3 consecutive days.

Reactions Associated with Intragam®P Use Post-Marketing
Haemolytic anaemia associated with the presence of anti-A antibodies has been reported following high dose therapy (>0.4 g/kg every 4 weeks) with Intragam® P in patients of blood group A or AB particularly in recipients with reduced bone marrow reserve or post haemopoietic stem cell transplantation.

Reactions Associated with Intravenous Immunoglobulins
The types of reactions that may occur include: malaise, abdominal pain, headache, chest-tightness, facial flushing or pallor, erythema, hot sensations, dyspnoea or respiratory difficulty, non-urticarial skin rash, cutaneous vasculitis, pompholyx on hands/palms, itching, tissue swelling, change in blood pressure, nausea or vomiting. Should any of these reactions develop during infusion of "TBSF" Human Immunoglobulin for Intravenous Use, the infusion should be temporarily stopped until the patient improves clinically (5 to 10 minutes) and then cautiously recommenced at a slower rate.

Some patients may develop delayed adverse reactions to intravenous immunoglobulin (IVIG) such as: nausea, vomiting, chest pain, rigors, dizziness, aching legs or arthralgia. These adverse reactions occur after the infusion has stopped but usually within 24 hours.

True hypersensitivity reactions to IVIG such as urticaria, angioedema, bronchospasm or hypotension occur very rarely. Should an anaphylactic reaction to "TBSF" Human Immunoglobulin for Intravenous Use develop, the infusion should be stopped and treatment instituted with adrenaline, oxygen, antihistamine and steroids.

Haemolytic anaemia and neutropenia have been reported in rare instances in association with IVIG treatment.

Mild and moderate elevations of serum transaminases (AST, ALT, gamma GT) have been observed in a small number of patients given IVIG. Such changes were transient and not associated with the transmission of hepatitis.

An aseptic meningitis syndrome (AMS) and thrombophlebitis have occurred in patients receiving IVIG (see **PRECAUTIONS**).

Thrombotic events have been reported in association with IVIG therapy. Rarely, renal dysfunction and acute renal failure have been reported (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

This product should be administered by a medical practitioner only.

Dosage

"TBSF" Human Immunoglobulin for Intravenous Use may be infused undiluted. "TBSF" Human Immunoglobulin for Intravenous Use may also be infused diluted with up to 2 parts of 0.9% saline or 5% glucose. The infusion should be commenced at the rate of 1 mL per minute. After 15 minutes the rate may be gradually increased to a maximum of 3 to 4 mL per minute over a further 15 minutes. Consideration should be given to reducing the rate of infusion in elderly patients and in patients with pre-existing renal disease.

A rate of infusion which is too rapid may cause flushing and changes in heart rate and blood pressure.

Replacement Therapy

The optimal dose and frequency of administration of "TBSF" Human Immunoglobulin for Intravenous Use must be determined for each patient. Freedom from recurrent bacterial infections is usually achieved with a serum IgG level above 5 g per litre. Most patients receive a dose of 0.2 to 0.6 g IgG per kilogram body weight per month, either as a single dose or as two equal doses at fortnightly intervals. Following initial diagnosis, higher doses (0.4 to 0.6 g IgG per kilogram body weight per month) may be required for several months to provide rapid protection against recurrent infections. Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state and the pre-infusion IgG level.

Immunomodulatory Therapy

Idiopathic Thrombocytopenic Purpura (ITP)

The optimal dose and frequency of administration of "TBSF" Human Immunoglobulin for Intravenous Use must be determined for each patient. Patients may receive a dose of up to a maximum total cumulative dose of 2 g IgG per kilogram body weight, over two to five days. Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state.

Kawasaki disease

The optimal dose and frequency of administration of "TBSF" Human Immunoglobulin for Intravenous Use must be determined for each patient. Patients should receive 1.6-2.0 g IgG per kilogram body weight, administered in divided doses over two to five days or 2 g IgG per kilogram body weight as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Allogeneic bone marrow transplantation

Treatment with "TBSF" Human Immunoglobulin for Intravenous Use may be used as part of the conditioning regime and after the transplant. The optimal dose and frequency of administration of "TBSF" Human Immunoglobulin for Intravenous Use should be individualised. A starting dose of 0.5 g IgG per kilogram body weight per week is recommended.

Administration
If the product appears to be turbid by transmitted light or contains any sediment, it must not be used, and the bottle should be returned unopened to the Distributor listed on the label. "TBSF" HUMAN IMMUNOGLOBULIN FOR INTRAVENOUS USE CONTAINS NO ANTIMICROBIAL AGENT. It must, therefore, be used immediately after opening the bottle; any unused portion should be discarded. Do not use if the solution has been frozen.

"TBSF" Human Immunoglobulin for Intravenous Use should be administered separately from other intravenous fluids or medications the patient might be receiving.

"TBSF" Human Immunoglobulin for Intravenous Use may be administered through any standard I.V. infusion giving set. The following procedure is recommended:

1. Allow the preparation to reach room temperature before use.
2. Remove the plastic cover from the seal.
3. Apply a suitable antiseptic to the exposed part of the rubber stopper and allow to dry.
4. Stand the bottle upright and insert the air vent needle vertically in one of the indentations of the stopper. It is preferable to use a long airway needle fitted with a filter. If not available, a short needle attached to a non-wettable filter may be used.
5. Clamp the tubing of the giving set and insert the needle at the upper end of the giving set vertically through another indentation of the stopper. Should the stopper become dislodged, do not use this bottle and discard the solution appropriately.
6. Invert the bottle and attach the hanger to a support approximately one metre above the patient.
7. Allow the tubing to fill by adjusting the clamp. Attach the giving set to the venous access device (cannula) and adjust the rate of flow.
8. When the bottle is empty, clamp the tubing and transfer the needle at the upper end of the giving set to a further bottle of "TBSF" Human Immunoglobulin for Intravenous Use.
9. Should leakage become evident during administration, cease the infusion and discard the solution appropriately. Recommence the infusion with a new bottle and giving set.

OVERDOSAGE
Overdosage may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with renal impairment.

PRESENTATION AND STORAGE CONDITIONS
This product is available in 50 and 200 mL vials containing 3 and 12 g of IgG and 5 and 20 g of maltose respectively.

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.
Do not use after the expiry date.

REFERENCES

1. George, JN et al: Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for The American Society of Hematology. Blood 88, 3-40, 1996.
2. The American Society of Hematology ITP Guideline Panel: Diagnosis and Treatment of Idiopathic Thrombocytopenic Purpura: Recommendations of the American Society of Hematology: Ann Intern Med 126, 319-326, 1997.

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“國血製劑益康”人類免疫球蛋白靜脈注射劑
"TBSF" Human Immunoglobulin for Intravenous Use

成分名稱 衛署菌疫輸字第 000841 號

人類免疫球蛋白靜脈注射劑

說明

本產品係配合行政院衛生署執行「推動我國血漿製劑方案」所製造，是由台灣血液基金會自國人自願、無償捐血者收集之血漿原料，經製備而得之人類免疫球蛋白靜脈注射劑。

“國血製劑益康”人類免疫球蛋白靜脈注射劑是一種無菌、不含防腐劑的溶液。每 100ml 當中含有 6g 人血蛋白質 和 10g 麥芽糖。溶液的 pH 值 為 4.25。添加的麥芽糖是用來達成溶液之等滲透壓性。至少 98% 蛋白質具有相同於免疫球蛋白 G 的電泳移動性，至少 90% 蛋白質是 IgG 單體和雙體。根據三個臨床前批次 (preclinical batches)，和四個臨床批次 (clinical batches) 報告，“國血製劑益康”人類免疫球蛋白靜脈注射劑所含的 IgG 亞型之分布情形，其平均值是 61% IgG1、36% IgG2、3% IgG3、1% IgG4。“國血製劑益康”人類免疫球蛋白靜脈注射劑的 IgA (Immunoglobulin A)含量極少，(通常< 0.025 mg/mL)。“國血製劑益康”人類免疫球蛋白靜脈注射劑用於靜脈注射。

“國血製劑益康”人類免疫球蛋白靜脈注射劑是由大量匯集的人類血漿，經過色層分析法分離純化而來。其蛋白質未經過任何化學或酵素作用改變過。其生產過程包括嚴格的特定步驟，以降低病毒傳染的可能性，包括，巴斯德氏消毒法 (60°C 加熱 10 小時)，以及以低 pH 處理。

注意事項

本品係由人類血漿製得，自人類血漿所製得之產品，可能存在著某些感染原，例如致病性之病毒和庫賈氏病 (Creutzfeldt-Jakob disease, CJD)之病原；藉由篩檢血漿之捐血者，檢驗某些現有病毒感染原標記，再經由去活化及，或去除某些病毒，即可降低此產品傳染感染原之危險性。惟縱然採取上述措施，此類產品仍有可能存在某些未知的感染原。因此注射本產品後，若有感染之病人，均應直接向診療醫師及製造廠或代理商報告。請與你的醫師討論使用此產品之風險及利益。

本產品製造過程所採用的方法，可有效地對抗含外套膜的病毒，如 HIV (人類免疫缺乏病毒)、B 型及 C 型肝炎病毒，及不含外套膜的 A 型肝炎病毒。這些方法對抗不具外套膜的 parvovirus B19 之效果可能有限，然而本產品含有獨特的抗體可直接對抗 parvovirus B19。

使用血漿製品時可考慮給予疫苗之注射。

“國血製劑益康”人類免疫球蛋白靜脈注射劑之臨床試驗係根據 Intragam®P。Intragam®P 係為由 CSL Limited 生產並在澳洲銷售之人類靜脈注射免疫球蛋白(IVIG)。

藥理學與藥物動力學

在每月一次，施以 Intragam®P 6 個月之後，對 11 個(9 個男性，年紀介於 28-76 歲之間)，患有原發性免疫不全症 (primary immunodeficiency disorder) 的病人，測定其 IgG 的穩定狀態動力學 (steady-state kinetic) 參數，劑量視個別病人而異，介於 0.35-0.53 g/kg。平均血清 IgG 濃度從谷底的 7.4±1.1 g/L，到高峰的 15.8±1.7 g/L。平均清除率是 4.1±0.8 mL/h。平均半衰期為 39.7±7.8 天。平均回復率 (注射 Intragam®P 之後，血清 IgG 濃度增加到預期濃度的百分比值) 為 44.0±2.0% (請參見「**臨床試驗**」章節)。

臨床試驗

原發性免疫不全症 (Primary Immune Deficiency)

對 35 個患有原發性免疫不全症的病人 (年紀介於 6-76 歲；男性 21 位)試驗 "Intragam®P"人類免疫球蛋白靜脈注射劑的有效性。每月一次施以靜脈注射人類免疫球蛋白靜脈注射劑，連續 6 個月，劑量視個別病人而異，介於 0.2-0.67 g/kg 之間。在這 6 個月期間，每個病人平均住院天數為 2.8±9.0。因為病況而沒去工作或上學的平均天數為 5.3±6.4。這些數字與其它靜脈注射用免疫球蛋白的歷史數據相仿。

原發性血小板缺乏性紫斑症 【Idiopathic Thrombocytopenic Purpura (ITP)】

對 17 個患有 ITP (6 個急性、11 個慢性) 的病人 (年紀介於 21-72 歲；男性 5 位)試驗 "Intragam®P"人類免疫球蛋白靜脈注射劑的有效性。每天一次施以靜脈注射人類免疫球蛋白靜脈注射劑，連續 1-3 天。人類免疫球蛋白靜脈注射劑的劑量視個別病人而異，累積劑量最高達到 2 g/kg。施以人類免疫球蛋白靜脈注射劑治療之後，其中有 13 個病人 (76.5%) 的血小板數目到達良好 ($50x10^9$/L ~ $150x10^9$/L)，或很好 (> $150x10^9$/L) 的標準，其血小板數目可維持在≥$50x10^9$/L 最久達到 35 天，平均是 17.24 天【95% 信賴區間 (CI) 10.35, 24.12】。這些數字與其它靜脈注射用免疫球蛋白的歷史數據相仿。

這兩次試驗中所發生的任何不良副作用，都記錄在 **「不良反應」** 章節之中。

適應症

"國血製劑益康"人類免疫球蛋白靜脈注射劑是 IgG 的替代治療用藥，適應症包括：

- 原發性免疫不全症 (primary immune deficiency)。
- 骨髓瘤 (myeloma)與慢性淋巴性白血病 (chronic lymphatic leukaemia)合併嚴重續發性免疫球蛋白缺乏(severe secondary hypogammaglobulinaemia)與復發性感染 (recurrent infections)。
- 伴隨復發性感染之後天性免疫不全症 (AIDS with recurrent infections)。

"國血製劑益康"人類免疫球蛋白靜脈注射劑也可用於改善免疫調節機能，適應症包括：

- 原發性血小板缺乏性紫斑症【Idiopathic Thrombocytopenic Purpura (ITP)】，高危險出血的成人或小孩 ITP 患者；或者，手術前用以修正血小板數目。
- 異體骨髓移植 (allogeneic bone marrow transplantation)。
- 川崎氏症 (Kawasaki Disease)。

敘述 IVIG 用於 ITP 之適當臨床使用的規範均有相關的文獻記載，應遵照以避免本血液產

品的不當使用[1,2]。

禁忌

對人類免疫球蛋白會產生真正過敏反應的病人，忌用“國血製劑益康”人類免疫球蛋白靜脈注射劑。

特殊警語

“國血製劑益康”人類免疫球蛋白靜脈注射劑只能以靜脈注射使用，尚未有其它使用途徑的評估。在極少的情況下，“國血製劑益康”人類免疫球蛋白靜脈注射劑有可能造成血壓急速降低，和嚴重過敏性反應 (anaphylaxis) 的臨床徵狀。因此，腎上腺素 (adrenaline) 和氧氣必須隨時準備妥當，以處理這類急性反應。

“國血製劑益康”人類免疫球蛋白靜脈注射劑含有少量 IgA。體內具有抗 IgA 抗體的病人，可能會引發過敏反應，特別是選擇性 IgA 缺乏症 (selective IgA deficiency) 病人。

有關與靜脈注射免疫球蛋白 (IVIG) 之使用後發生的無菌性腦膜炎【aseptic meningitis syndrome (AMS)】，雖然不常發生，但是有過這樣的報告。這些症狀通常在使用 IVIG 之後數小時到兩天之內發生，其病徵包括，嚴重頭痛、頸背僵硬、困倦、發燒、畏光 (photophobia)、眼球移動觸痛、噁心、嘔吐。腦脊髓液 (cerebrospinal fluid, CSF) 分析常會發現白血球增多現象 (pleocytosis)，且多為顆粒性細胞 (granulocytic series)，腦脊髓液的蛋白質濃度也會增加。發生這些徵狀的病人，必須接受仔細的神經學檢查，包括腦脊髓液分析，以排除腦膜炎是否有其它原因造成。AMS 比較有可能與高劑量的 IVIG (2 g/kg) 治療有關係，停止 IVIG 治療後，AMS 會在幾天之內緩解，不留後遺症。

偶而會有一些報告指出，病人在使用 IVIG 產品後，發生腎臟機能障礙和急性腎臟衰竭。比較有可能發生這些症狀的高危險病患包括，既有的腎臟功能不全、糖尿病、年齡 65 歲以上、體液容量減少 (volume depletion)、敗血病 (sepsis)、副蛋白血症 (paraproteinemia)、以及同時正在服用具腎毒性 (nephrotoxic) 藥物的病人。大部分這些事件都與藥物裡所含的蔗糖有關係。雖然 “國血製劑益康”人類免疫球蛋白靜脈注射劑不含蔗糖，以下的預防措施還是應該遵循：病人在 IVIG 注射給藥之前，必須供應適當的水分，以及勿使用超過建議的劑量，並且對有可能發生腎臟衰竭危險性的病人，必須監控其腎臟功能，如果腎臟功能惡化，必須考慮停止 IVIG 的治療。

因為產品內含有抗 A、抗 B、及偶有的抗 D 或其它抗紅血球的抗體存在，有人報告過，在使用高劑量靜脈注射免疫球蛋白後，球蛋白抗體直接試驗 (direct antiglobulin test)會呈陽性反應，及發生紅血球溶血 (haemolysis)現象，這種紅血球敏感症可能引起紅血球交叉比對試驗 (crossmatching) 的困難度，以及造成暫時性的溶血性貧血。

A 型或 AB 型血型的病人接受高劑量 IVIG 治療(每四週大於 0.4g/kg)，特別是那些降低骨髓量或造血幹細胞移植後，較容易被感染。

病人接受高劑量 IVIG 治療(每四週大於 0.4g/kg)，應該預備注射已決定的 ABO 血型。臨床上證實出現明顯溶血治療期間應監控血紅素。

血栓形成的事件已被報導和 IVIG 治療有關。風險因素包含高齡、不動性、心臟排出量損害、增加血漿黏度的適應症，如高三酸甘油脂血症及漿細胞惡病質症。

對於酸鹼平衡調節機制正常的病人，其血中的緩衝力量能夠中和最大劑量造成的酸性負擔，即使該劑量是以快速的靜脈注射注入。如果病人的酸鹼平衡調節機制不良者，包括新生兒在內，這類藥劑可能造成的酸性負擔必須加以考量。

高劑量（大於 0.4 g/kg)，長時間的給藥(6 小時以上)後，可能會在注射處引起血栓性靜脈炎 (thrombophlebitis)。

病人輸注 IVIG 有下列情形者可能會有較高產生副作用的頻率，包含那些本質上較輕微的。

- 第一次輸注
- 離上一次輸注有一段長時間
- 較罕見的為更換 IVIG 產品

IVIG 的反應容易與輸注速率有關，且大多發生在輸注的第一個小時。建議在輸注的過程中規率地監控病人的生命跡象與一般狀態。

致癌性，基因毒性和損害生殖能力

“國血製劑益康”人類免疫球蛋白靜脈注射劑在致癌性，基因毒性和損害生殖能力的潛在毒性，還沒有相關的研究。CSL 的血漿產品製劑是否有這方面的影響，尚未有相關研究報告。

懷孕與哺乳期的使用

懷孕與哺乳期間使用本藥品的安全性，還沒有相關的臨床研究。因此，對懷孕與哺乳婦女施用 “國血製劑益康”人類免疫球蛋白靜脈注射劑要特別小心。免疫球蛋白會分泌到母乳裡面。就我們的臨床經驗，免疫球蛋白不會對懷孕過程、胎兒、或新生兒造成傷害。

與其他藥物的交互作用

“國血製劑益康”人類免疫球蛋白靜脈注射劑與其它藥物的交互作用情形，還沒有相關研究報告。

經輸入而獲得的抗體 (被動免疫抗體)，會干擾人體對活性減毒疫苗的反應。因此，接種疫苗，例如小兒麻痺或麻疹疫苗，必須延到給藥後約三個月再施打；相同的道理，施打疫苗後，也必須至少等兩個星期以上，才能使用免疫球蛋白。

葡萄糖估計的干擾情形

“國血製劑益康”人類免疫球蛋白靜脈注射劑裡的麥芽糖可能會干擾血中葡萄糖的測量，導致高估血中葡萄糖含量。假如此葡萄糖測量是用於引導治療，低血糖症可能會發生。只有特定使用葡萄糖去氫酵素的檢驗方法會被影響，所以當監控輸注“國血製劑益康”人類免疫球蛋白靜脈注射劑病人的葡萄糖含量時，應注意葡萄糖量尺及/或檢驗試

劑製造商的資訊，以確認麥芽糖不會干擾血中葡萄糖的判讀。

不良反應

未注射過免疫球蛋白的病人可能會有較高產生副作用的頻率，包含那些本質上較輕微的。病人對靜脈注射免疫球蛋白的反應，大多與注射的速度有關，而且都發生在注射後的第一個小時內，病人的生命跡象和一般狀況，在注射期間應該隨時加以監控。

臨床試驗中與"Intragam®P"有關的反應

原發性免疫不全症 (Primary Immune Deficiency)

在臨床試驗當中，在 35 個接受**"Intragam®P"**的病人身上觀察到以下的不良副作用(括弧內數字為發生該不良副作用的病人人數)：頭痛 (8)、偏頭痛 (migraine) (2)、貧血 (2)、噁心 (2)、眩暈 (vertigo) (1)、嗜中性白血球減少症 (neutropenia) (1)、血小板減少症 (thrombocytopenia) (1)、疲勞倦怠 (1)。病人的每個月人類免疫球蛋白靜脈注射劑，劑量介於 0.2-0.67 g/kg 體重。

原發性血小板缺乏性紫斑症 【Idiopathic Thrombocytopenic Purpura (ITP)】

在臨床試驗當中，在 17 個接受"Intragam®P"的病人身上觀察到以下的不良副作用(括弧內數字為發生該不良副作用的病人人數)：頭痛 (10)、直接古姆氏試驗 (Direct Coombs' test) 陽性 (5)、溶血 (haemolysis) (4)、噁心 (3)、寒顫 (rigors) (3)、發燒 (2)、肌痛 (myalgia) (1)、嗜睡 (somnolence) (1)、腹痛 (1)、嘔吐 (1)、高血壓 (1)、潮紅 (1)、溶血性貧血 (haemolytic anaemia) (1)、白血球減少 (leukopenia) (1)、網狀細胞增多 (reticulocytosis) (1)、淋巴球減少 (lymphopenia) (1)、過敏反應 (1)、熱潮紅 (1)、以及注射處發炎 (1)。病人的人類免疫球蛋白靜脈注射劑，靜脈注射劑量介於 0.66-2 g/kg 體重，每天一次，連續注射 1-3 天。

上市後使用與 Intragam®P 有關的反應

A 型或 AB 型血型的病人接受高劑量 Intragam®P 治療後(每四週大於 0.4g/kg)，被報導有與出現 anti-A 抗體有關的溶血性貧血，特別是那些降低骨髓量或造血幹細胞移植後。

與靜脈注射免疫球蛋白有關的反應

可能發生的反應類型包括：身體不適、腹痛、頭痛、胸悶 (chest tightness)、臉部潮紅或臉色蒼白、紅斑、躁熱感 (hot sensations)、呼吸困難 (dyspnoea or respiratory difficulty)、非蕁麻皮膚疹 (non-urticarial skin rash)、皮膚脈管炎、手掌/腳掌汗疱、發癢、組織腫大、血壓改變、噁心或嘔吐。如果在靜脈注射"國血製劑益康"人類免疫球蛋白靜脈注射劑時發生任何這種反應，必須暫停注射動作，直到病人臨床狀況改善 (5 到 10 分鐘)，然後再小心地以緩慢一點的速度恢復注射。

有些病人對靜脈注射免疫球蛋白 (IVIG) 產生的副作用反應可能會有延遲發生的現象，例如，噁心、嘔吐、胸痛、寒顫、暈眩、腿痛或關節痛。這些副作用會發生在注射結束以後，但通常在 24 小時之內。

對 IVIG 產生嚴重的過敏反應，例如蕁麻疹 (urticaria)、血管性水腫 (angioedema)、支

氣管痙攣 (bronchospasm)、或低血壓，很少發生。如果對 “國血製劑益康”人類免疫球蛋白靜脈注射劑產生過敏反應，注射動作應該停止，並且對病人施以腎上腺素 (adrenaline)、氧氣、抗組織氨和類固醇治療。

雖然極少發生，還是有一些與 IVIG 治療有關的溶血性貧血 (haemolytic anaemia)，以及嗜中性白血球減少症 (neutropenia) 發生的報告。

少數接受 IVIG 治療的病人，發生血清之氨基轉移酶 (transaminases： AST, ALT, gamma-GT) 輕微到中度的濃度提高現象，這些改變都是暫時性的，而且與肝炎的感染無關。

接受 IVIG 治療的病人當中，曾有報告發生無菌性腦膜炎【aseptic meningitis syndrome (AMS)】 和靜脈炎 (thrombophlebitis) (請參見「**特殊警語**」章節)。

血栓形成的事件已被報導和 IVIG 治療有關。雖然極少發生，但是有人報告過，腎臟機能障礙和急性腎臟衰竭的發生 (請參見「**特殊警語**」章節)。

劑量及用法

本藥限由醫師使用

劑量

“國血製劑益康”人類免疫球蛋白靜脈注射劑可以不經稀釋施打，也可以用兩倍量的 0.9% 生理食鹽水或 5% 葡萄糖水稀釋後再注射。注射速度應該以每分鐘 1mL 開始，持續 15 分鐘以上，然後注射速度可以漸增，直到 15 分鐘後達最高的每分鐘 3-4mL。應考慮降低高齡病人及有腎臟病病人的輸注速率。

太快的注射速度會造成臉部潮紅、心跳和血壓的改變。

補充治療 (Replacement therapy)

“國血製劑益康”人類免疫球蛋白靜脈注射劑的最適劑量和給藥頻率必須視個別病人而定。血清中 IgG 濃度保持在 5g/L 以上，通常就能夠避免復發性的細菌感染。大部分病人每個月接受的劑量介於 0.2-0.6 g IgG /kg 體重。可以單一劑量施給，也可以平分兩次劑量隔週施給。為了使復發性感染的病人得到最快速的保護效果，病人經過初步診斷之後，可能需要高一點的劑量 (每個月 0.4-0.6 g IgG /kg 體重)，持續治療數個月。使用劑量和給藥頻率的調整，須靠經驗決定，而且必須視病人的臨床狀況及其注射前 IgG 濃度而定。

免疫調節療法 (Immunomodulatory therapy)

原發性血小板缺乏性紫斑症 【Idiopathic Thrombocytopenic Purpura (ITP)】
“國血製劑益康”人類免疫球蛋白靜脈注射劑的最適劑量和給藥頻率必須視個別病人而定。病人在 2 到 5 天之內接受的最高累積劑量可達 2 g IgG /kg 體重。使用劑量和給藥頻率的調整純靠經驗決定，而且必須視病人的臨床狀況而定。

川崎氏症 (Kawasaki disease)
“國血製劑益康”人類免疫球蛋白靜脈注射劑的最適劑量和給藥頻率必須視個別病人而定。病人可以 2 到 5 天內接受 1.6-2.0 g IgG /kg 體重的劑量，分次施給，或以單一次劑量 2.0 g IgG /kg 體重施給。病人必須同時施以乙醯水楊酸治療。

異體骨髓移植 (Allogeneic bone marrow transplantation)
可以將 “國血製劑益康”人類免疫球蛋白靜脈注射劑當作調整療法 (conditioning regime) 的一部份，也可以用於移植之後。 “國血製劑益康”人類免疫球蛋白靜脈注射劑的最適劑量和給藥頻率必須視個別病人而定。建議的起始劑量為每週 0.5 g IgG /kg 體重。

使用說明
如果發現本產品有混濁現象或含有沉澱物，切勿使用，並將產品原封不動退回給標籤上標示的代理商。**“國血製劑益康”人類免疫球蛋白靜脈注射劑不含任何抗微生物劑**，因此打開瓶子之後必須立即使用，任何未用完的藥劑都必須丟棄，切勿使用曾經被冷凍過的溶液。

“國血製劑益康”人類免疫球蛋白靜脈注射劑必須與病患接受的其它靜脈注射液或用藥分開使用。

“國血製劑益康”人類免疫球蛋白靜脈注射劑可以經由標準的一般靜脈注射套組給藥。我們建議以下的程序：

1. 靜待本產品回復到室溫再使用。
2. 移除塑膠封套。
3. 將曝露在外的橡皮塞做適當消毒，並靜待其乾燥。
4. 將點滴瓶直立，從點滴瓶橡皮塞的一個凹痕處，垂直插入排氣針，最好是一個附有過濾器的長針，不然，也可以使用一個附有不沾水濾器的短針。
5. 夾緊點滴管，以位於點滴管終端的針頭，垂直插入點滴瓶橡皮塞的另一個凹處。如果橡皮塞有移位或鬆動情形，請停止使用該點滴瓶，並小心丟棄裡面的溶液。
6. 倒轉點滴瓶，把它吊在一個適當的點滴架上，大約高於病人一公尺的高度。
7. 調整夾子，使點滴管充滿溶液。接通點滴管到靜脈，裝妥銜接套管 (cannula)，並調整適當流速。
8. 當點滴瓶空了以後，夾住點滴管，將點滴管終端的針頭轉插到一瓶新的 “國血製劑益康”人類免疫球蛋白靜脈注射劑。
9. 給藥當中，如果發生明顯滲漏，停止點滴並小心丟棄瓶中溶液。請更換一個新的藥瓶與新的點滴套組使用。

過量使用
使用過量可能造成輸液過多(fluid overload) 和高黏度血症 (hyperviscosity)，尤其是在老年人和患有腎臟疾病的病人。

包裝型式
本產品有兩種大小包裝：50 和 200mL 藥瓶，每瓶分別含有 3g 和 12g 的 IgG 免疫球蛋

白，以及 5 g 和 20g 的麥芽糖。

儲存

應儲存於 2°C~8°C 之間 (冷藏，切勿冷凍)。請避光儲存。超過效期切勿再使用。

文獻

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製造廠

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