ACQUIRED HAEMOPHILIA

Hyate:C Prescribing Information

References:

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2. The use of Antihemophilic factor (porcine) – Hyate:C in the treatment of acquired hemophilia. (Submission to US FDA to extend product licence no. 1014). Data on file with Porton Speywood Ltd., Wrexham, UK.
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Further information can be obtained from
Porton Products Limited, Porton House,
Vanwall Road, Maidenhead,
Berkshire, SL6 4UB. ENGLAND.
Telephone 0628 771417. Telefax 0628 770211.

NAME OF PRODUCT: HYATE:C

PRESENTATION: Hyate:C is a highly purified freeze dried concentrate of porcine antihaemophilic factor (Factor VIII:C). Hyate:C is in the form of a white lyophilised powder for reconstitution with 20ml Water for Injections B.P. per vial. Each vial contains between 400-700 units of Factor VIII:C. The assayed amount of activity is stated on the label.

USES: Hyate:C is intended for the treatment or prevention of bleeding in patients with haemophila A who have inhibitors to Human Factor VIII:C.

DOSAGE AND ADMINISTRATION: The dosage of Hyate:C required for control of bleeding varies for individual patients. The required dose is dependent upon:

1. The weight of the patient;
2. The activity of the antibody against Hyate:C;
3. The type of haemorrhage and desired plasma Factor VIII:C level.

The required dose is determined by administering a preliminary dose of Hyate:C and assaying the post-infusion level of Factor VIII:C in the patient's plasma. According to the response, dosage can then be increased or decreased for subsequent infusions. It is commonly observed that recovery of Factor VIII:C increases during a course of treatment, possibly as a result of saturation of circulating antibody. It is therefore desirable to monitor pre and post infusion levels of Factor VIII:C for each dose.

An estimate of the preliminary dose of Hyate:C recuired for the initial infusion can be made in the following ways:

1. If the patient's antibody titre against Hyate:C is not known, but the anti-human Factor VIII:C titre is less than than 50 Bethesda Units ml, an initial dose of 25-50 units/Kg body weight for a moderately severe joint or muscle bleed, or 100 units/Kg body weight, for a major life threatening bleed is recommended.
2. If the patient's antibody titre against Hyate:C is known or can be determined, a prediction of the dose of Hyate:C required to neutralise the antibody can be made using the formula:
   Neutralising dose = Plasma volume (ml) x antibody titre (Bethesda units/ml).
   The incremental dose must then be added to this neutralising dose to increase the Plasma Factor VIII level by the desired amount. This increment can be calculated by assuming that 1 unit of Hyate:C per Kg body weight will give rise to a 1.5 units/decilitre increase in Plasma Factor VIII:Cactivity.[2]

Example:

Patient Body weight	= 55 Kg
Haematocrit	= 0.5 litre/litre
Antibody Titre	= 3 Bethesda units/ml
Desired Factor VIII:C Level	= 40% of normal i.e. 40 units Factor VIII/dl of Plasma.
Dose-Response Relationship	= 1 unit of Hyate:C per Kg body weight will give rise to a 1.5 units/decilitre increase in plasma Factor VIII:C activity.
Average Blood Volume	= 80 ml/Kg.

(i) **Plasma Volume**
Patient's body weight x Average Blood Volume x (1 minus Haematocrit)
i.e. Plasma Volume = 55 x 80 x (1 - 0.5) = 2,200 mls

(ii) **Neutralising Dose**
Plasma Volume x Antibody Titre ie Neutralising Dose = 2,200 x 3 = 6,600 units

(iii) **Incremental Dose**
Desired plasma Factor VIII:C level x patient's Body Weight / Dose-Response Relationship

ie. Incremental Dose = $\frac{40 \times 55}{1.5}$ = 1,466 units

(iv) **Total Dose** = Neutralising Dose + incremental Dose
ie. Total Dose = 6,600 + 1,466 = 8,066 units.

3. If the patient's antibody titre against Hyate:C is not known, but the anti-human Factor VIII:C level is greater than 50 Bethesda units/ml, an initial dose of 100-250 units/Kg body weight is suggested followed by determination of the Plasma Factor VIII:C level.[1]
4. If a patient has previously been treated with Hyate:C, this may provide a guide to his likely response, and therefore assist in estimation of the preliminary dose.

Subsequent Dose Administration
Following administration of the preliminary dose, if the recovery of Factor VIII:C in the patient's plasma is not sufficient, a further dose should be administered. If the recovery after the second dose is still insufficient a third and higher dose may prove effective.

Deterination of the activity of the inhibitor against Hyate:C
A modification of the Bethesda assay[3] is recommended. Hyate:C should be diluted to 1 unit per ml in haemophilic plasma and used as a substrate in the Bethesda assay.

Reconstitution and Administration:
1. Warm the unopened vials of Hyate:C to between 20°C and 37°C.
2. Clean the exposed central portion of the rubber stopper with antiseptic immediately prior to piercing.
3. Using a sterile needle and syringe slowly inject 20 ml of water for Injections B.P. into the vial.
4. Withdraw the needle and shake the vial gently, avoiding frothing, until the powder is completely dissolved. This usually takes less than five minutes.
5. Withdraw the solution into the syringe using a filter needle.
7. Replace the filter needle with a sterile injection needle and administer intravenously at a rate of not more than 2-5 ml per minute.

CONTRA-INDICATIONS:
There are no known contra-indications to Hyate:C.

WARNINGS ETC:

Acute Infusion reactions
On rare occasions Hyate:C may give rise to acute infusion reactions, such as anaphylactic shock.
Adrenaline, hydrocortisone and facilities for resuscitation should be available in case these reactions occur.

Mild Infusion reactions
Hyate:C may give rise to reactions such as fever, chills, headaches, nausea, vomiting and skin rashes. These reactions are more common after the first infusion of a course of treatment, and tend to lessen in frequency and severity as further infusions are given. Hydrocortisone and/or antihistamine may alleviate these effects and may be prescribed as a precautionary measure.

Immune response to Hyate:C
Infusion of Hyate:C may be followed by a rise in plasma levels of inhibitor to both human and porcine Factor VIII:C Inhibitor levels to both porcine and human Factor VIII:C should therefore be monitored after treatment.

Effect on the Platelet Count
A significant fall in the patient's platelet count occurs on rare occasions after infusion of Hyate:C. However, monitoring of the platelet count during the treatment period is recommended.

PHARMACEUTICAL PRECAUTIONS: Hyate:C should be stored at a temperature of −15°C to −20°C and should be used before the expiry date stated on the package. Reconstituted Hyate:C must not be stored and should be used within three hours.

LEGAL CATEGORY: Prescription only.

PACKAGE QUANTITIES: Vials contain not less than 400 units of Porcine Factor VIII:C HYATE:C. The number of units in each vial is printed on the vial label.

FURTHER INFORMATION: The ease of reconstitution of Hyate:C in 20ml Water for Injections B.P. makes it suitable for syringe administration facilitating high dose therapy.

PRODUCT LICENCE NUMBER (UK):
3070/0007.

PORTON

H104

HYATE:C IN ACQUIRED HAEMOPHILIA

"Excellent cover during operation"[2]

"Satisfactory haemostasis throughout"[2]

"BLEEDING STOPPED PROMPTLY"[2]

HYATE:C FIRST IN ACQUIRED HAEMOPHILIA

The incidence

The occurrence of acquired haemophilia, the spontaneous development of autoantibodies to the Factor VIII:C molecule, is not as rare as previously imagined. Although less common than Factor VIII:C inhibitors arising in congenital haemophiliacs, acquired haemophilia may develop in post-partum women, as a drug reaction for example to penicillin, ampicillin and phenytoin or in association with underlying auto-immune disease such as systemic lupus erythematosus and rheumatoid arthritis.

In Green and Lechner's 1981 survey[1] of 215 acquired haemophilia patients there was an even distribution of male and female patients and the majority (73%) were over 50 years of age. In 53% of the patients there was no apparent cause for the development of an inhibitor other than old age.

The need

Such acquired haemophilia patients experience severe bleeding episodes in the same way as congenital haemophiliacs. The Green and Lechner study showed that:

87% of the patients suffered major bleeds.

22% died as a result.

These results clearly demonstrate the need for an effective treatment.

High Efficacy with Hyate:C[2]

– FDA approved for first line therapy in acquired haemophilia.

– Clinical benefit obtained in all but one patient.

EUROPEAN DATA

Nature of Treatment	Units	No. of Infusions	Clinician's Comments
Large haematoma	9,000	4	Excellent
Surgical operation to remove haemophilic pseudotumor	270,600	NR	Satisfactory haemostasis throughout (1)
Cover for caesarian section	NR	9	Successful haemostasis
Epistaxis	1,200	1	Bleeding stopped
Thigh haematoma + haematuria	20,100	9	Excellent. Bleeding stopped promptly
Haemarthrosis (knee)	5,700	3	Good
Retroperitoneal haemorrhage	63,500	21	Fair
Bruising, large haematoma & limb bleeds	23,900	5	Good
US DATA			
Emergency major surgery	54,000	14	Excellent
Post-operative bleeding	153,000	27	Excellent
Gastro-intestinal bleed + bleed in hand	16,400	2	Fair
Dental cover	7,000	1	Excellent
Hematuria	13,500	2	No reduction in hematuria
Gastro-intestinal bleed	16,000	3	Good (1)
Cover for hysterectomy	152,700	36	Excellent cover during operation
Post-operative bleeding	303,800	35	Fair – bleeding stabilised
Subcutaneous & gastro-intestinal bleeding	56,800	NR	Good. Bleeding halted
Retroperitoneal bleed	21,000	3	Fair (2)

NR = Not recorded

No Evidence of Virus Transmission[3,4]

"...other advantages of Hyate:C include its high purity and the fact that it does not transmit hepatitis or acquired immune deficiency syndrome (AIDS)."

(Lusher, 1987.)

"Thus porcine concentrate is well-suited for the management of patients who have <u>not</u> been exposed previously to those infections through use of human plasma products, a category that includes most previously non-haemophiliac patients."

(Kasper and Ewing, 1986.)

Low antibody cross-reactivity[2,5]

- range 0-14% (mean 5.7%).
- 6 patients had no cross-reactivity.

"...the majority of high titre spontaneous factor VIII inhibitors exhibit little cross-reactivity with porcine factor VIII and can be treated successfully with this product."

(Hultin & Hennessey, 1989.)

Low Anamnestic Response[2]

- in 15 out of 18 patients there was no elevation in antibody titre.
- only one patient showed significant anamnesis.
- antibody titres declined in 7 patients.

Low incidence of infusion reactions[2]

- 98% of infusions were free from reactions. (171/175).
- 4 mild reactions – treatments completed beneficially.