SPEYWOOD LABORATORIES LIMITED

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THE USE OF HYATE:C (PORCINE FACTOR VIII:C) IN THE TREATMENT OF ACQUIRED HEMOPHILIA AND A REPORT ON THE INCIDENCE OF INFUSION REACTIONS DURING THE CLINICAL STUDY OF ANTIHEMOPHILIC FACTOR (PORCINE) HYATE:C IN THE UNITED STATES OF AMERICA

CANADIAN PRODUCT LICENCE NO. 219 DIN NO. 738859

Dr. P. N. Robinson, Technical Manager
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May 1988
Volume 1

PURPOSE OF THIS SUBMISSION

THIS DOCUMENT IS SUBMITTED AS SUBSTANTIATING EVIDENCE TO SUPPORT THE APPLICATION FOR CHANGES IN THE CURRENT CANADIAN LICENCE NO. 219 (DIN NO. 738859) FOR HYATE:C (PORCINE FACTOR VIII:C)

IN ORDER TO:-

1. INCLUDE AS AN INDICATION THE PRIMARY TREATMENT OF POTENTIAL AND OVERT HEMORRHAGIC EPISODES IN PATIENTS WITH ACQUIRED HEMOPHILIA

   AND

2. TO DELETE THE RESTRICTIONS ON THE USE OF THE PRODUCT WHICH RELATE TO IT ONLY BEING USED IN A LIFE OR LIMB THREATENING SITUATION FOLLOWING THE FAILURE OF ALL OTHER TREATMENT OPTIONS.

I N D E X

I N D E X CONTINUED

PAGE

PROPOSED REVISION OF PRODUCT MONOGRAPH/PACKAGE INSERT FOR HYATE:C (PORCINE FACTOR VIII:C)

HYATE:C (PORCINE FACTOR VIII:C)
PRODUCT MONOGRAPH/PACKAGE INSERT - PROPOSED DELETIONS

The present insert dated 30th April 1987 which follows has been marked in ORANGE to highlight the proposed deletions.

These are only in Paragraph 3 of the INDICATIONS section.

DELETIONS	REPORT REFERENCE JUSTIFICATION
"Use of Hyate:C should be limited to patients suffering life or limb threatening bleeds or requiring essential surgery"	Part Three Pages 229 to 254
"Its use, should be limited to critical situations where alternative therapy has been exhausted or would likely prove ineffective" at the end of the paragraph	

There are NO deletions from the back of the package insert.

Proposed ADDITIONS are detailed and highlighted on the proposed new package insert which then follows on Pages 4, 5a and 5b.

TEXT OF CURRENT PRODUCT MONOGRAPH/PACKAGE INSERT WITH PROPOSED DELETIONS HIGHLIGHTED

Insert
HYATE:C
PORCINE FACTOR VIII:C

INDICATIONS Hyate:C is a highly purified freeze dried concentrate of porcine antihemophilic factor (Factor VIII:C) in the form of a white lyophilized powder.

Hyate:C is intended for the treatment or prevention of bleeding in patients with hemophilia A who have antibodies to Factor VIII:C.

Use of Hyate:C should be limited to patients suffering life or limb-threatening bleeds or requiring essential surgery. Its use should be limited to critical situations where alternative therapy has been exhausted or would likely prove ineffective.

Hyate:C treatment is not normally indicated in patients with an antibody titre of less than 5 Bethesda units/ml (BU/ml) against human Factor VIII:C and is likely to be ineffective in patients with an antibody titre of greater than 50 BU/ml against human Factor VIII.

However, if a patient has an antibody titre of greater than 50 BU/ml against human Factor VIII:C the activity of the antibody against porcine Factor VIII should be determined. An antibody titre of less than 15-20 BU/ml against porcine Factor VIII:C indicates suitability for treatment with Hyate:C.

CLINICAL PHARMACOLOGY The development of antibodies to human Factor VIII constitutes a serious clinical complication in the management of haemophilia A. It occurs in 8—14% of treated haemophiliacs[1] who then become resistant to further therapy. Antibodies may also arise spontaneously in the elderly or in patients with auto-immune or collagen disorders.[2]

The clinical efficacy of Hyate:C was found to be directly related to the presence of measurable levels of Factor VIII:C in the patient's plasma after infusion. Thus the patients for whom Hyate:C is likely to prove an effective form of therapy can be identified as those patients whose antibody against porcine Factor VIII is of a sufficiently low level that it can be neutralized by infusion of Hyate:C so that a measurable level of Factor VIII can be achieved in the plasma.

Inhibitors to both human Factor VIII:C and Hyate:C have been determined pre-treatment and at regular intervals during and post-treatment, whenever feasible. It has been observed that antibodies in patients as measured prior to treatment with Hyate:C are almost invariably less reactive with Hyate:C than with human Factor VIII concentrate (i.e. the anti-Hyate:C titre is usually lower than the anti-human Factor VIII:C titre).[3]

In a number of cases, the course of Hyate:C treatment has been preceded by, or included, treatment with human blood, or blood products. In these patients, it is not possible to determine the direct effect of Hyate:C on the inhibitor level. However, in those cases where Hyate:C has been given alone, the effect on the inhibitor titre has been closely observed; in many of these patients there has been no evidence whatsoever of an anamnestic rise in antibody level. The immunogenic potential of Hyate:C would thus appear to be low, i.e. anamnestic responses are generally less common and less marked after therapy with porcine than human Factor VIII.[4] However, the occurrence of an elevation of the inhibitor titre has been recorded[5] and this possibility must not be discounted.

Clinical responses to Hyate:C have been strikingly good in most cases and in a number of instances, Hyate:C has proved effective in achieving haemostasis in inhibitor patients, when current conventional treatment had failed.[6] Many patients have received multiple courses of Hyate:C therapy; as many as 25 separate bleeding episodes have been treated in one patient without evidence of loss of clinical or laboratory efficacy or increased tendency to adverse reactions.

CONTRAINDICATIONS AND WARNINGS There are no known contraindications to Hyate:C.

Acute Infusion Reactions On rare occasions Hyate:C administration has been associated with anaphylaxis.

Adrenaline, Hydrocortisone and facilities for resuscitation should be available in case such a reaction occurs.

Mild Infusion Reactions Hyate:C may give rise to reactions such as fever, chills, headache, 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 both during and after treatment.

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

ADVERSE REACTIONS AND PRECAUTIONS Being of animal origin, Hyate:C is potentially antigenic and must therefore be administered with care. It is strongly advised that each course of treatment should be preceded by a test dose of 100 i.u. prior to administration of the full dose. The patient should be observed in the interim period for signs of hypersensitivity.

Hyate:C should be infused slowly (not more than 2—5 ml/min). Concurrent treatment with antihistamine and steroids is advised as a precautionary measure. Adrenaline and hydrocortisone should be immediately available in case of severe anaphylactic shock.[7]

Other adverse reactions observed to date have been notably delayed in onset (1—2 hours post infusion) but of the type frequently associated with infusion of any plasma protein.

Fever, chills, nausea, headache and skin rashes have all been reported, but these reactions have been transient and relatively mild.[8]

DOSAGE AND ADMINISTRATION The dosage of Hyate:C required for control of bleeding varies for individual patients, but is dependent upon the patient's weight, the level of circulating antibody and the type of hemorrhage and desired plasma Factor VIII level.

The correct dose for an individual patient can be 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, the dosage can then be either 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. This is of particular importance during long courses of treatment when variation in the patient's antibody level may give rise to considerable variation in the recovery of Factor VIII:C in the plasma.

HYATE:C (PORCINE FACTOR VIII:C)
PRODUCT MONOGRAPH/PACKAGE INSERT REVISION INCLUDING ADDITIONS

The proposed draft of the new package insert is on the following pages, but it has been enlarged for clarity of reading. When approved the package insert will be printed on fine paper size 8" by 5" as previously.

Proposed additions have been highlighted in YELLOW and can be summarised as follows:-

PROPOSED ADDITIONS	REPORT REFERENCE JUSTIFICATION
Indications Add to the end of paragraph 2: "and also for previously non-hemophilic patients with spontaneously acquired inhibitors to human Factor VIII:C"	Report Part one & two Pages 6 - 228
Replace paragraph 3 with: "Use of Hyate:C is indicated for patients who are bleeding or who are to undergo surgery".	See references cited above.
Add on extra paragraph after paragraph 3. "Hyate:C has not been known to transmit hepatitis or human immunodeficiency virus (HIV) It may therefore be justified to consider Hyate:C (Porcine Factor VIII:C) as a primary treatment option in acquired inhibitor patients, or other patients who have never been exposed to human viral infections through human blood products." due to the insertion of an additional reference in this paragraph all subsequent references become 2 - 12.	See references cited above
Add a final paragraph Clinical Pharmacology "No evidence of human viral infection has been reported with the use of Hyate:C	Clinician's letters Pages 9 + 10. Also clinical reports see Vol.2 Page 99 Dr.Kasper and 152 Dr. Lusher

There are no further changes in the text following Clinical Pharmacology through to the end of the "PACKAGE QUANTITY" information

Reference number 1 has been added "Lusher J.M. Factor VIII Inhibitors - Etiology, Characterisation, Natural History and Management. Annals of the New York Academy of Sciences (1987) 509 96".

All subsequent references are as the original but become 2 - 12.

The date of printing to be determined following approval.

Note: When these changes are approved the same changes will be made to the text of the French/Canadian package insert.

Insert
HYATE:C
PORCINE FACTOR VIII:C

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Use of Hyate:C is indicated for patients who are bleeding or who are to undergo surgery.

Hyate:C has not been known to transmit hepatitis or human immunodeficiency virus (HIV).[1] It may therefore be justified to consider Hyate:C (Porcine) Factor VIII:C as a primary treatment option in acquired inhibitor patients, or other patients who have never been exposed to human viral infections through human blood products.

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Inhibitors to both human Factor VIII:C and Hyate:C have been determined pre-treatment and at regular intervals during and post-treatment, whenever feasible. It has been observed that antibodies in patients as measured prior to treatment with Hyate:C are almost invariably less reactive with Hyate:C than with human Factor VIII concentrate (i.e. the anti-Hyate:C titre is usually lower than the anti-human Factor VIII:C titre).[4]

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DOSAGE AND ADMINISTRATION The dosage of Hyate:C required for control of bleeding varies for individual patients, but is dependent upon the patient's weight, the level of circulating antibody and the type of hemorrhage and desired plasma Factor VIII level.

The correct dose for an individual patient can be 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, the dosage can then be either 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. This is of particular importance during long courses of treatment when variation in the patient's antibody level may give rise to considerable variation in the recovery of Factor VIII:C in the plasma.

A.—Preliminary Dose Administration An estimate of the preliminary dose of Hyate:C required 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 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.[10]
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) × antibody titre (BU/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 in plasma Factor VIII:C activity.[11]

   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 × Average Blood Volume × (1 minus Haematocrit) i.e. Plasma Volume = 55 × 80 × (1—0.5) = 2,200 mls

   (ii) **Neutralising Dose** Plasma Volume × Antibody Titre i.e. Neutralising Dose = 2,200 × 3 = 6,600 units

   (iii) **Incremental Dose**

   $$\frac{\text{Desired plasma Factor VIII:C level} \times \text{Patient's Body Weight}}{\text{Dose-Response Relationship}}$$

   i.e. Incremental dose = $\frac{40 \times 55}{1.5}$ = 1466 units

   (iv) **Total Dose** = Neutralising Dose + Incremental Dose i.e. Total Dose = 6,600 + 1466 = 8066 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.[10]
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

B.—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, higher dose should be administered. If recovery after the second dose is still insufficient a third and higher dose may prove effective. As previously noted, the recovery of Factor VIII:C tends to improve with successive doses.

Determination of the Activity of the Inhibitor against Hyate:C A modification of the Bethesda assay[12] is recommended. Hyate:C should be diluted to 1 unit per ml in hemophilic plasma and used as a substrate in the Bethesda assay.

Reconstruction 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 a syringe, slowly inject 20ml of Sterile Water for Injection U.S.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 5 minutes.
5. Withdraw the solution into a syringe using a filter needle.
6. Replace the filter needle with a sterile injection needle and administer intravenously at a rate of not more than 2—5 ml per min.

STORAGE PRECAUTIONS Hyate C should be stored at a temperature of minus 15°C to minus20°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 3 hours.

PACKAGE QUANTITIES Vials containing not less than 400 units of Porcine Factor VIII:C.

REFERENCES

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