HEMOFIL®M ANTIHAEMOPHILIC FACTOR, (HUMAN), METHOD M, MONOCLONAL PURIFIED.

Part V A

DOSAGE FORM

Part V A. DOSAGE FORM

V A:1. Packaging

Antihaemophilic Factor (Human), Method M, HEMOFIL®M is to be marketed as a lyophilised product in a clear Type I E.P. glass container with a blue chlorobutyl rubber closure, and a protective aluminium cap with flip-off top.

The product will be sold according to the approximate International Units of AHF activity contained in each bottle: three codes are envisaged:

Nominally 250 IU/bottle
Nominally 500 IU/bottle
Nominally 1000 IU/bottle

Each of these codes will be supplied in a unit carton which contains the lyophilised concentrate and "Directions for Use" package leaflet. A separate carton will contain the following ancillary products:

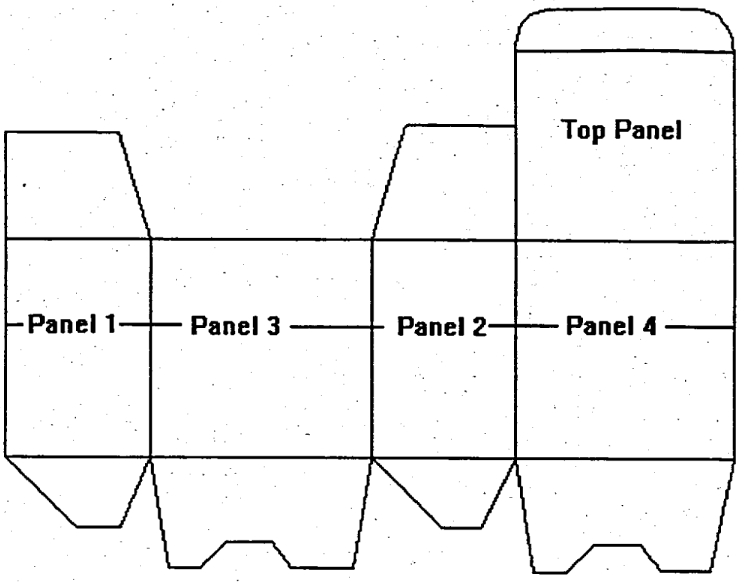
a) An E.P. Type I glass container holding 10mL of Water for Injections E.P. (diluent).
b) A sterile, double-ended needle.
c) A sterile filter needle.
d) A 10mL plastic syringe.
e) A 23 ga. mini-infusion set.

The Water for Injections diluent (a) is licenced under Baxter Healthcare Ltd., PL.0116/0024.

The sterile devices (b) will be manufactured by Companies and Facilities registered under the UK Department of Health, Manufacturers Registration Scheme (Sterile Products Category).

V A:1.1. Proposed Text for HEMOFIL®M Unit Carton

Carton Diagram



A. TOP PANEL:

List No. XD060-XXX Contents: 1 bottle

HEMOFIL®M 250/500/1000 I.U.
Antihaemophilic Factor
(Human), Method M, Monoclonal Purified

B. TOP SECTION SIDE PANELS:

XD060-XXX Contents: 1 bottle
10ml size, dried

Baxter Wordmark / Hyland®

HEMOFIL®M 250/500/1000 I.U.
Antihaemophilic Factor
(Human), Method M,
Monoclonal Purified

C. BOTTOM SECTION, SIDE PANELS:

PANEL 1: Store This Package Between 2 and 8°C.

Reconstitute at room temperature with 10mL Water for Injections Ph.Eur. Commence administration within one hour after reconstitution. Do not refrigerate after reconstitution. Do not use if solution is incomplete or if a clot forms on reconstitution.

This lot contains XXX International Units of AHF Activity per bottle.

Lot No.:

Expiry Date:

PANEL 2: Blank

PANEL 3: Content: One bottle of 10mL
Antihaemophilic Factor (Human).

Lyophilised Powder For Intravenous
Administration after Reconstitution

Contains no preservative.

Warnings: The risk of transmitting
hepatitis or other viral diseases may
be present. Read direction insert
and use as directed by physician.
Safely dispose of any unused solution
and administration accessories.

Keep out of reach of children.

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Baxter Healthcare Ltd.,
Caxton Way, Thetford,
Norfolk, IP24 3SE.

Marketing Authorisation Number:

PL.0116/0236,0237,0238 | POM |

PANEL 4: Blank

V A:1.2. Accessories Carton

The carton containing the accessory products will contain the following information:

Baxter Wordmark / Hyland®

Accessory carton for HEMOFIL®M

Antihaemophilic Factor (Human),
Method M, Monoclonal Purified

Contents: One bottle of 10mL Water for Injections Ph.Eur. (PL.0116/0024); one double-ended needle; one filter needle, one 10mL syringe and one 23 ga. mini-infusion set.

Keep out of reach of children.

Store below 25°C. Avoid freezing to prevent damage to the diluent bottle.

Lot No: Expiry Date:

® Registered Trademark

POM

Baxter Healthcare Ltd.,
Caxton Way, Thetford,
Norfolk, IP24 3SE.

V A:2. Label Copy

V A:2.1. Proposed text for HEMOFIL®M bottle

Baxter Wordmark / Hyland® 10mL size, dried

HEMOFIL®M

Antihaemophilic Factor (Human), Method M,
Monoclonal Purified 250/500/1000 I.U.

Lyophilised Powder For Intravenous Administration
after Reconstitution

Store Between 2 and 8°C

Do not refrigerate after reconstitution and commence administration within one hour after reconstitution.

Warnings: The risk of transmitting hepatitis or other viral diseases may be present. Read direction insert and use as directed by physician.

This bottle contains XXX I.U. of AHF activity.

Lot No.: Expiry Date:

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Baxter Healthcare Ltd.,
Caxton Way, Thetford, IP24 3SE.

Marketing authorisation number:PL.0116/0236,0237,0238
List number: XD060-XXX

POM

V A:2.2. Proposed Text for Diluent Bottle

Baxter Wordmark / Hyland® 10mL

Diluent (Water For Injections Ph.Eur) for reconstitution of HEMOFIL®M, Antihaemophilic Factor (Human), Method M, Monoclonal Purified

Store Below 25°C. Avoid freezing to prevent damage to container.

Lot No.: Expiry Date:

®Registered Trademark

Baxter Healthcare Ltd., PL.0116/0024
Caxton Way, Thetford,
Norfolk, IP24 3SE.

POM

V A:3

Proposed Text for Package Direction Insert

Baxter Wordmark / Hyland®

HEMOFIL®M Antihaemophilic Factor (Human), Method M, Monoclonal Purified Nominally 250/500/1000 I.U.

Presentation:

HEMOFIL®M , Antihaemophilic Factor (Human), Method M is a sterile, non-pyrogenic, lyophilised human Antihaemophilic Factor (factor VIII, factor VIII:C, AHF) preparation for reconstitution in Water for Injections diluent. For intravenous administration.

Each bottle of HEMOFIL®M, Antihaemophilic Factor (Human), Method M is labelled with the AHF content expressed in International Units (I.U.) per bottle.

HEMOFIL®M, , Antihaemophilic Factor (Human), Method M is formulated to contain the following other ingredients:

Albumin (Human)	100	mg/bottle
Sodium Chloride	81	mg/bottle
Calcium Chloride.$2H_2O$	5.3	mg/bottle
Polyethylene Glycol 3350	10	mg/bottle
Histidine	77.5	mg/bottle

HEMOFIL®M, Antihaemophilic Factor (Human), Method M is prepared by the Method M process from pooled human plasma by immunoaffinity chromatography utilizing a murine monoclonal antibody to factor VIII:C, followed by an ion exchange chromatography step for further purification.

The Method M process also includes treatment with an organic solvent {tri (n-butyl) phosphate} and detergent (octoxynol 9) designed to reduce the risk of transmission of hepatitis and other viral diseases.

HEMOFIL®M, Antihaemophilic Factor (Human), Method M is supplied in a single dose bottle, with a 10mL bottle of Water for Injections diluent, a double ended needle for reconstitution, a filter needle, a 10mL plastic syringe and a 23 ga. mini-infusion set.

Therapeutic Indications:

HEMOFIL®M, Antihaemophilic Factor (Human), Method M is indicated in acquired and congenital factor VIII deficiency for the prevention and control of haemorrhagic episodes. Clear identification of the clotting deficiency as one of factor VIII is essential.

The product can be of significant therapeutic value in patients with factor VIII inhibitors.

It should be noted that HEMOFIL®M, Antihaemophilic Factor (Human), Method M is not suitable for use in the treatment of Von Willebrands Disease.

Contraindications:

None known.

Warnings, Precautions For Use:

Use during Pregnancy and Lactation:

Animal reproduction studies have not been conducted with Antihaemophilic Factor (Human). It is also not known whether Antihaemophilic Factor (Human) can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Antihaemophilic Factor (Human) should be given to a pregnant woman only if clearly needed.

Undesirable Effects:

i) As with the administration of any protein, allergic reactions may be encountered with the use of antihaemophilic factor preparations. Early signs of hypersensitivity reactions include fever, chills, nausea, hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician if any of these symptoms occur.

ii) With products derived from human blood, the transmission of infectious diseases by transmission of pathogens of unknown nature e.g., Non-A and Non-B hepatitis cannot be ruled out.

This product is prepared from pooled units of human plasma which have been individually tested and found nonreactive for Hepatitis B surface antigen (by third generation test) and negative for antibody to Human Immunodeficiency Virus (HIV-1)* by F.D.A. approved tests and have been shown to have alanine aminotransferase (ALT) levels not exceeding two times the upper limit of normal.

The manufacturing process includes an organic solvent {tri (n-butyl) phosphate} and detergent (octoxynol 9) step designed to reduce the risk of transmission of hepatitis and other viral diseases. As a result of this procedure and considering current scientific knowledge, the risk of transmitting the causitive agent of Immune Deficiency Syndrome (AIDS) can almost certainly be excluded.

iii) With factor VIII products derived from human blood, inhibitor formation may occur.

* To be updated when HIV-2 and HCV testing implemented.

Instructions For Dosage and Administration:

Dosage Estimation:

The following formulae can be used to calculate the appropriate dose required for a given in vivo response (a) or the in vivo response from a given dose (b). These dosage formulae are presented for reference and as guidelines. The amount of factor VIII that an individual haemophiliac requires for normal haemostasis varies with circumstances and with the patient. Exact dosage determinations should be based on the medical judgement of the physician regarding the circumstances, condition of the patient, degree of factor VIII deficiency, and the level of AHF to be achieved.

a) Units required =

Body weight (kg) x 0.5 units/kg x desired factor VIII increase (% of normal)

Example: 70 kg x 0.5 units/kg x 50 = 1,750 units

b) Expected factor VIII increase (% of normal) =

$$\frac{\text{units administered}}{\text{Body weight (kg) x 0.5 units/kg}}.$$

Example: $\frac{1{,}750 \text{ units}}{70 \text{ kg x } 0.5 \text{ units/kg}} = 50\%$

The response factor used in the preceding formulae (one unit factor VIII increases the in vivo factor VIII level by 2%) is derived from a study of in vivo recovery and survival of factor VIII in 56 haemophiliacs involving 15 different lots of HEMOFIL®M, Antihaemophilic Factor (Human), Method M injected at a nominal 50 units per kg body weight dose. The mean highest recovery point above the mean pre-infusion baseline was 2.0 units/ dL per unit/kg body weight. The mean in vivo half-life in this study was 14.0 hours.

If not prescribed otherwise, the following dosage schedule is recommended:

In Haemorrhagic Episodes:

	Required minimal factor VIII activity in the blood (in % of normal or units/dL plasma)	Duration of treatment
minor haemorrhagic episodes	10 - 20	2-3 days or until bleeding stops
more serious haemorrhage	20 - 30	3-4 days
serious haemorrhage	30 - 60	7-15 days or until wound heals

For Surgical Procedures:

	Required minimal factor VIII activity in the blood (in % of normal or units/dL plasma)	Duration of substitution therapy
minor surgery	10 - 20	until wound heals
moderately severe operations or serial tooth extractions	20 - 40	until wound heals
major surgery	50 - 100 (pre-and post-operative)	1-3 days or until wound heals

The careful control of the substitution therapy is especially important in major operations.

Although dosage can be estimated by the calculations given above, it is strongly recommended that whenever possible appropriate laboratory tests be performed on the patient's plasma at suitable intervals to ensure that adequate factor VIII levels have been reached and are maintained. If factor VIII fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected.

The inhibitor can be identified and quantified by the appropriate laboratory tests. With the quantitative determination the number of factor VIII units which are neutralised by either 1 mL or the calculated total patient plasma are established. The final dosage is then calculated by adding the normal dosage to the amount of factor VIII required to neutralise the inhibitor.

When inhibitors are present, the whole blood clotting time may give a better dosage estimate than the measurement of circulating factor VIII.

Directions For Use:

The preparation is to be administered intravenously after reconstitution with the provided water for injection diluent (see also "Reconstitution" and "Injection" sections). Disposable plastic syringes should be used with this product.

It is recommended that administration commences within 1 hour after reconstitution. The reconstituted material may not be refrigerated. The preparation can be administered at a rate of up to 10 mL per minute.

The pulse rate should be determined before and during administration of HEMOFIL®M, Antihaemophilic Factor (Human), Method M. Should a significant increase occur, reducing the rate of administration or temporarily ceasing the injection usually allows the symptoms to disappear promptly.

Reconstitution:

Check labelled expiry date prior to reconstitution. Do not use HEMOFIL®M, Antihaemophilic Factor (Human), Method M if expiry date has been passed.

1) Bring unopened bottles of diluent and dry concentrate up to room temperature (20-30°C). This temperature needs to be maintained until dissolution is complete.

   Caution: When using a waterbath, the stopper and closures must not come in contact with water.

2) Remove caps from concentrate and diluent bottles to expose central portion of rubber stoppers.

3) Cleanse stoppers with germicidal solution.

4) Remove protective covering from one end of double-ended reconstitution needle not touching the exposed needle. Then insert exposed needle through diluent stopper.

Caution: To be able to withdraw the diluent completely, the needle should be inserted so that the tip only just penetrates the rubber septum.

5) Using the same aseptic technique as above, remove protective cover from the other end of the double-ended needle. Invert diluent bottle over upright concentrate bottle, then rapidly insert free end of the needle through the concentrate bottle stopper at its centre. The vacuum in the concentrate bottle will draw in the diluent.

6) Disconnect the two bottles by removing needle from the concentrate bottle. Swirl gently until all material is dissolved. Be sure that the concentrate is completely dissolved, otherwise active material will be removed by the filter.

Injection:

1) After reconstitution of the concentrate as described above, insert filter needle (attached to a syringe) through the bottle stopper.

2) Inject air into bottle and withdraw solution into syringe.

3) Remove syringe and inject solution intravenously through the administration set.

4) If a patient is to receive more than 1 bottle of HEMOFIL®M, Antihaemophilic Factor (Human), Method M the same syringe may be used. However, a new filter needle has to be used for each bottle of HEMOFIL®M.Antihaemophilic Factor (Human), Method M

Pharmaceutical Precautions:

Do not administer HEMOFIL®M, Antihaemophilic Factor (Human), Method M simultaneously with other intravenous preparations.

When stored refrigerated (2-8°C) HEMOFIL®M, Antihaemophilic Factor (Human), Method M is stable for the period indicated by the expiration date on the label. Within this period HEMOFIL®M, Antihaemophilic Factor (Human), Method M may be stored at room temperature (not more than 30°C) for up to 6 months. Do not freeze as this may damage the container for the diluent.

Commence administration of reconstituted product within 1 hour of reconstitution. Do not refrigerate reconstituted product.

Name and Address of Marketing Authorisation Holder:

Baxter Healthcare Ltd.,
Caxton Way,
Thetford, Norfolk, IP24 3SE.

Marketing Authorisation Number(s):

PL.0116/0236 - 0238

Name and Address of Manufacturer:

Baxter Healthcare Corporation,
Hyland Division,
Glendale, CA 91203, USA.

and

B-7860 Lessines, Belgium.

Date of Leaflet Preparation:

March 1992.

V A:4 Proposed Text for Data Sheet

FOR THE ATTENTION OF THE MEDICAL PROFESSION.

Data Sheet	BAXTER/HYLAND Wordmarks
HEMOFIL®M	Antihaemophilic Factor (Human), Method M, Monoclonal Purified

Presentation:

HEMOFIL®M is a sterile, non-pyrogenic, lyophilised human Antihaemophilic Factor (factor VIII, factor VIII:C, AHF) preparation for reconstitution in Water for Injections diluent. For intravenous administration.

Each bottle of HEMOFIL®M is labelled with the AHF content expressed in International Units (I.U) per bottle.

HEMOFIL®M is formulated to contain the following other ingredients:

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HEMOFIL®M is prepared by the Method M process from pooled human plasma by immunoaffinity chromatography utilizing a murine monoclonal antibody to factor VIII:C, followed by an ion exchange chromatography step for further purification.

The Method M process also includes treatment with an organic solvent {tri (n-butyl) phosphate} and detergent (octoxynol 9) designed to reduce the risk of transmission of hepatitis and other viral diseases.

Uses:

HEMOFIL®M is indicated in acquired and congenital factor VIII deficiency for the prevention and control of haemorrhagic episodes. Clear identification of the clotting deficiency as one of factor VIII is essential.

The product can be of significant therapeutic value in patients with factor VIII inhibitors.

It should be noted that HEMOFIL®M is not suitable for use in the treatment of Von Willebrands Disease.

Dosage and Administration:

Dosage Estimation:

The following formulae can be used to calculate the appropriate dose required for a given in vivo response (a) or the in vivo response from a given dose (b). These dosage formulae are presented for reference and as guidelines. The amount of factor VIII that an individual haemophiliac requires for normal haemostasis varies with circumstances and with the patient. Exact dosage determinations should be based on the medical judgement of the physician regarding the circumstances, condition of the patient, degree of factor VIII deficiency, and the level of AHF to be achieved.

a) Units required =

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b) Expected factor VIII increase (% of normal) =

$$\frac{\text{units administered}}{\text{Body weight (kg) x 0.5 units/kg}}.$$

Example: $\frac{1{,}750 \text{ units}}{70 \text{ kg x } 0.5 \text{ units/kg}} = 50\%$

The response factor used in the preceding formulae (one unit factor VIII increases the in vivo factor VIII level by 2%) is derived from a study of in vivo recovery and survival of factor VIII in 56 haemophiliacs involving 15 different lots of HEMOFIL®M injected at a nominal 50 units per kg body weight dose. The mean highest recovery point above the mean pre-infusion baseline was 2.0 units/dL per unit/kg body weight. The mean in vivo half-life in this study was 14.0 hours.

If not prescribed otherwise, the following dosage schedule is recommended:

In Haemorrhagic Episodes:

	Required minimal factor VIII activity in the blood (in % of normal or units/dL plasma)	Duration of treatment
minor haemorrhagic episodes	10 - 20	2-3 days or until bleeding stops
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major surgery	50 - 100 (pre-and post-operative)	1-3 days or until wound heals

The careful control of the substitution therapy is especially important in major operations.

Although dosage can be estimated by the calculations given above, it is strongly recommended that whenever possible appropriate laboratory tests be performed on the patient's plasma at suitable intervals to ensure that adequate factor VIII levels have been reached and are maintained. If factor VIII fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected.

The inhibitor can be identified and quantified by the appropriate laboratory tests. With the quantitative determination the number of factor VIII units which are neutralised by either 1 mL or the calculated total patient plasma are established. The final dosage is then calculated by adding the normal dosage to the amount of factor VIII required to neutralise the inhibitor.

When inhibitors are present, the whole blood clotting time may give a better dosage estimate than the measurement of circulating factor VIII.

Directions For Use:

The preparation is to be administered intravenously after reconstitution with the provided water for injection diluent (see also "Reconstitution" and "Injection" sections). Disposable plastic syringes should be used with this product.

It is recommended that administration commences within 1 hour after reconstitution. The reconstituted material may not be refrigerated. The preparation can be administered at a rate of up to 10 mL per minute.

The pulse rate should be determined before and during administration of HEMOFIL®M. Should a significant increase occur, reducing the rate of administration or temporarily ceasing the injection usually allows the symptoms to disappear promptly.

Contraindications, Warnings, Precautions etc:

Contraindications

None known.

Warnings, Precautions For Use:

Use during Pregnancy and Lactation:

Animal reproduction studies have not been conducted with Antihaemophilic Factor (Human). It is also not known whether Antihaemophilic Factor (Human) can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Antihaemophilic Factor (Human) should be given to a pregnant or lactating woman only if clearly needed.

Undesirable Effects:

i) As with the administration of any protein, allergic reactions may be encountered with the use of antihaemophilic factor preparations.

Early signs of hypersensitivity reactions include fever, chills, nausea, hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician if any of these symptoms occur.

ii) With products derived from human blood, the transmission of infectious diseases by transmission of pathogens of unknown nature e.g., Non-A and Non-B hepatitis cannot be ruled out.

This product is prepared from pooled units of human plasma which have been individually tested and found nonreactive for Hepatitis B surface antigen by third generation test and negative for antibody to Human Immunodeficiency Virus (HIV-1)* by F.D.A. approved tests and have been shown to have alanine aminotransferase (ALT) levels not exceeding two times the upper limit of normal.

The manufacturing process includes an organic solvent {tri (n-butyl) phosphate} and detergent (octoxynol 9) step designed to reduce the risk of transmission of hepatitis and other viral diseases. As a result of this procedure and considering current scientific knowledge, the risk of transmitting the causitive agent of Immune Deficiency Syndrome (AIDS) can almost certainly be excluded.

iii) With factor VIII products derived from human blood, inhibitor formation may occur.

* To be updated when HIV-2 and HCV testing implemented.

Pharmaceutical Precautions:

Do not administer HEMOFIL®M simultaneously with other intravenous preparations.

When stored refrigerated (2-8°C) HEMOFIL®M is stable for the period indicated by the expiration date on the label. Within this period HEMOFIL®M may be stored at room temperature (not more than 30°C) for up to 6 months. Do not freeze as this may damage the container for the diluent.

Commence administration of reconstituted product within 1 hour of reconstitution. Do not refrigerate reconstituted product.

Legal Category:

Prescription Only Medicine.

Package Quantities:

Antihaemophilic Factor (Human), HEMOFIL®M, is available as single dose bottles. Each bottle is labelled with the potency in International Units, and is provided with 10 mL of Water for Injections Ph.Eur., a double-ended reconstitution device, a filter spike, a 10 mL syringe and a 23 Ga. miniset.

Unit Size	Approximate Activity	Code Number
10 mL	250 IU/Bottle	FD-060-XXX
10 mL	500 IU/Bottle	FD-060-XXX
10 mL	1000 IU/Bottle	FD-060-XXX

Further Information

Water for Injections Ph.Eur. diluent licenced under PL.0116/0024.

Product Licence Number: PL.0116/0236 - 0238

Product Authorisation Numbers: PA.167/X/X

Date of Preparation: March 1992

BAXTER wordmark

BAXTER Healthcare Ltd.,
Thetford, Norfolk, England.

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