Class Monograph
Haemodialysis Solutions

Description:

This monograph applies to products in the form of liquid concentrate that are intended to be used for acute and chronic haemodialysis. The medicinal ingredients, their concentrations and combinations are restricted to those specified in this monograph. Full justification supported with information in the public domain should be provided for any deviations in ingredients, concentrations and indications. The medicinal ingredients must be identified on product labelling by the names given in this monograph.

Types of Haemodialysis Solutions (Ingredients and Concentrations):

1. *Concentrated solutions with acetates or lactates*

   Several formulations of concentrated solutions are used. The concentrations of the components in the solutions are such that after dilution (usually in a 1:34 ratio) to the stated volume the concentrations of the components per litre as usually in the following ranges:

Table 1	Expression in millimoles	Expression in milliequivalents
Sodium	130.0 - 145.0	130.0 - 145.0
Potassium	0 - 3.0	0 - 3.0
Calcium	0 - 2.0	0 - 4.0
Magnesium	0 - 1.2	0 - 2.4
Acetate/Lactate	32.0 - 45.0	32.0 - 45.0
Chloride	90.0 - 120.0	90.0 - 120.0
Glucose	0 - 12.0	n/a

2. *Concentrated acidic solutions*

Several formulations of concentrated solutions are used. The concentrations of the components in the solutions are such that after dilution to the stated volume and before neutralisation with Sodium Bicarbonate the concentrations of the components per litre are usually in the following ranges:

Table 2	Expression in millimoles	Expression in milliequivalents
Sodium	80.0 - 110.0	80.0 - 110.0
Potassium	0 - 3.0	0 - 3.0
Calcium	0 - 2.0	0 - 4.0
Magnesium	0 - 1.2	0 - 2.4
Acetic acid	2.5 - 10.0	2.5 - 10.0
Chloride	90.0 - 120.0	90.0 - 120.0
Glucose	0 - 12.0	n/a

Solutions of Sodium Bicarbonate or solid Sodium Bicarbonate may be added immediately before use to a final concentration of not more than 45 millimoles per litre. The concentrated solution of Sodium Bicarbonate is supplied in a separate container. The concentrated acidic solutions and the concentrated solution of Sodium Bicarbonate are diluted and mixed immediately before using a suitable device. Alternatively, solid Sodium Bicarbonate may be added to the diluted solution.

Pharmaceutical Quality:

The minimum chemistry and manufacturing data requirements for haemodialysis solutions are outlined in Section XII of the Drugs Directorate Guidelines, *Preparation of Drug Identification Number Submissions* and are as follows:

1. the name and address of the manufacturer of the medicinal ingredient(s)
2. the name and address of the manufacturer (and importer, if applicable) of the finished product; if the manufacturer is located in a foreign country, evidence of compliance with Canadian GMP
3. a copy of the Master Formula with detailed manufacturing directions for a typical batch size. The document should contain the quantitative list of all ingredients expressed in mg/mL and in kg/batch, the grade of all ingredients, the filling instructions and all in-process controls. This should also include the method of filterization/sterilization of the bulk solution and finished product. If filters are used for sterilization, details of the method used to test their integrity before and after filtration should be submitted. The method of washing/sterilization and depyrogenation of each packaging component should be provided. Note: Each ingredient declared in the quantitative formulation portion of the application form should be identical to the listing in the Master Formula.
4. for ingredients that do not meet a Schedule B pharmacopoeial standard, provide specifications (tests with analytical methods and limits)
5. finished product specifications which include tests with analytical methods and limits (refer to pharmacopoeial standards, where applicable)
6. *Certificate of Analysis* for one lot of the finished product packaged in the proposed container/closure system; where applicable, numerical results should be reported instead of 'conforms' and/or 'complies'
7. a description of all packaging materials in direct contact with the product and all labelling materials
8. packaging materials specifications, equivalent to current pharmacopoeial requirements which should include tests with analytical methods and limits
9. the expiration date that will be used with a statement that supporting stability studies are available; for expiration periods exceeding 24 months, stability data should be submitted

Special Notes:

Pharmacopoeial standards for formulated single and multiple ingredients haemodialysis preparations that are contained in Schedule B publications are shown in Appendix I. Note that this list is intended only as a guide and is not necessarily current or all inclusive.

Labelling:

This monograph describes those requirements that are specific to this group of drug products. They can be found in the *Food and Drugs Act and Regulations*, including the publications referred to in Schedule B to the Act, and in the Drugs Directorate Guidelines, *Labelling of Drugs for Human Use*, and are as follows:

Inner and Outer Label:

1. The proper or common name should be declared immediately preceding or following the brand name, of any, in type size not less than one half the size of that of the brand name.
2. A standard of manufacture should be declared in close proximity to the brand name.
3. The notation "sterile", "stérile" should appear in both official languages if the product is required to be sterile.
4. The name and address of the manufacturer of the drug product should appear.
5. A lot number should be assigned to the drug product and preceded by one of the following expressions: Lot number, Lot No., Lot and (L).
6. Adequate directions for use of the drug product should be provided and should include the following information and/or statements:
    i. Concentrated solution is to be diluted immediately before use
    ii. Dilution to be made
    iii. Volume taken for use is to be measured accurately
    iv. Ionic formula for the diluted solution in mmol/L and stating that it is supplied by the concentrated solution only
    v. Any unused solution to be discarded
    vi. Sodium bicarbonate to be added before use where applicable
    vii. Pharmacological classification or indications for use and/or route of administration
7. The medicinal ingredients should be declared quantitatively in g/L and mmol/L
8. The declaration of expiration date should be in the format YEAR-MONTH and preceded by one of the following terms: Expiration, Expiration Date and Exp. The expiration date itself may be expressed in full or refer to the guideline for acceptable abbreviations.
9. The net amount of the drug in the container should be declared in terms of volume.
10. The drug identification number assigned for the drug product should be shown in a clear manner and preceded by the designation "DIN".
11. Storage conditions should be provided.

Special Notes:

Detailed calculations for the ionic concentrations of the diluted solution should be submitted with the DIN submission.

Procedures:

Each solution will require a Drug Identification Number (DIN) to be sold in Canada, regardless of how small the difference in electrolyte concentration. A sponsor must submit a completed DIN submission with the minimum data requirements as outlined in this class monograph for each haemodialysis product.

In cases where a sponsor has a series of products with the identical ingredients in variable concentrations and the concentrations are within the ranges outlined in Table 1 (Concentrated solutions with acetates or lactates), or Table 2 (Concentrated acidic solutions), the sponsor is required to submit a complete submission for one of the products. Such a submission must contain a completed *Drug Submission Application* form (HPB 3011), including proposed Canadian labelling, a completed *DIN Submission Certification*, and complete chemistry and manufacturing data including a copy of the Master Formula. A complete review will be conducted on this submission.

For other submissions the sponsor must provide a completed *Drug Submission Application* form (HPB 3011), including the proposed Canadian labelling, and a completed *DIN Submission Certification*, but may cross-reference the data provided for the complete submission and submit a letter signed by the company representative stating that all aspects of the application, with the exception of the specified concentrations are identical to the original submission.

References:

Handbook of Dialysis, 2nd Edition

Appendix I

Pharmacopoeial Haemodialysis Preparations

Proper Name	
Haemodialysis Solutions	BP 1993, Addendum 1996
Solutions for Haemodialysis	BP 1993
Potassium Chloride	BP 1993
Calcium Chloride	BP 1993
Magnesium Chloride	BP 1993
Sodium Bicarbonate	BP 1993