IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0167/098/003
Case No: 2063572

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Baxter Healthcare Limited

Caxton Way, **Thetford**, **Norfolk IP24 3SE**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

CLINIMIX N12G20E, solution for infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/05/2009** until **11/12/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

CLINIMIX® N12G20E, solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CLINIMIX® N12G20E is packaged in a dual compartment plastic bag containing respectively an amino acid solution with electrolytes and a glucose solution with calcium.

The injectable amino acid solution contains 15 L-amino acids (8 essential amino acids) needed for the protein synthesis.

The amino acid profile is the following:
- Essential amino acids/Total amino acids = 41.3%
- Essential amino acids/Total nitrogen = 2.83
- Branched chain amino acids/Total amino acids = 19 %

The quantitative composition of CLINIMIX® N12G20E is the following:

	7% Amino acid solution with electrolytes	20% Glucose solution with calcium
Active ingredients		
L-Leucine	5.11 g/l	
L-Phenylalanine	3.92 g/l	
L-Methionine	2.80 g/l	
L-Lysine (as L-Lysine chlorhydrate)	4.06 g/l (5.07 g/l)	
L-Isoleucine	4.20 g/l	
L-Valine	4.06 g/l	
L-Histidine	3.36 g/l	
L-Threonine	2.94 g/l	
L-Tryptophan	1.26 g/l	
L-Alanine	14.49 g/l	
L-Arginine	8.05 g/l	
Glycine	7.21 g/l	
L-Proline	4.76 g/l	
L-Serine	3.50 g/l	
L-Tyrosine	0.28 g/l	
Sodium acetate, $3H_2O$	5.15 g/l	
Dibasic potassium phosphate	5.22 g/l	
Sodium chloride	1.88 g/l	
Magnesium chloride $6H_20$	1.02 g/l	
Glucose (as monohydrate glucose)		200 g/l (220 g/l)
Calcium chloride, $2H_20$		0.66 g/l

For excipients, see section 6.1

After mixing of the contents of both compartments, the composition of the binary mixture, for all the available bag sizes, is the following:

	N12G20E **1 l**	**N12G20E** **1.5 l**	**N12G20E** **2 l**
Nitrogen (g) Amino acids (g) Glucose (g)	5.8 35 100	8.7 53 150	11.6 70 200
Total calories (kcal) Glucose calories (kcal)	540 400	810 600	1080 800
Sodium (mmol) Potassium (mmol) Magnesium (mmol) Calcium (mmol) Acetate (mmol) Chloride (mmol) Phosphate as HPO_4^{--} (mmol)	35 30 2.5 2.3 60 40 15	53 45 3.8 3.4 90 60 23	70 60 5.0 4.5 120 80 30
pH Osmolarity (mOsm/l)	6 1060	6 1060	6 1060

3 PHARMACEUTICAL FORM

Solution for infusion.

Appearance prior to reconstitution: The aminoacid and glucose solutions are clear and colourless or slightly yellow
Appearance after reconstitution: Clear and colourless or slightly yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Parenteral nutrition when oral or enteral alimentation is impossible, insufficient or contra-indicated.
For patient undergoing long-term parenteral nutrition, the addition of a lipid emulsion to CLINIMIX® in order to supply both calories and essential fatty acids is possible.

4.2 Posology and method of administration

4.2.1 Dosage and rate of infusion

The dosage is chosen according to the metabolic needs, the energy expenditure and the clinical status of the patient.

In adults, the requirements range from 0.16 g of nitrogen/kg/d (approximately 1 g of amino acid/kg/d) to 0.35 g of nitrogen/kg/d (approximately 2 g of amino acid/kg/d).
In infants, the requirements range from 0.35 g of nitrogen/kg/d (approximately 2 g of amino acid/kg/d) to 0.45 g of nitrogen/kg/d (approximately 3 g of amino acid/kg/d).

The calorie requirements range from 25 kcal/kg/d to 40 kcal/kg/d, depending on the nutritional status of the patient and the degree of catabolism. In some cases, the addition of a lipid emulsion to CLINIMIX® is recommended.

The rate of administration should be adjusted according to the dosage, the characteristics of the infused solution, the total volume intake per 24 hours and the duration of the infusion. The infusion time should be higher than 8 hours.

The maximum infusion rate is 2.5 ml/kg/hour or 150 ml/hour to 175 ml/hour (for a patient weighing 60 kg to 70 kg).
The maximum daily dose is 40 ml/kg or 2400 ml to 2800 ml (for a patient weighing 60 kg to 70 kg).

4.2.2 Routes of administration

The amino acid and glucose solutions should be infused via a central vein.
The amino acid and glucose solutions are usually administered together with a lipid emulsion. Solutions or mixtures with an osmolarity above 800 mOsm/l should be infused via a central vein.

4.3 Contraindications

- Known hypersensitivity to any of the ingredients.
- Renal failure in the absence of haemodialysis, haemofiltration or haemo-dia-filtration.
- Severe liver disease.
- Amino acid metabolism disorders
- Metabolic acidosis, hyperlactataemia
- Adrenal insufficiency
- Hyperosmolar coma
- General contra-indications of an infusion therapy such as pulmonary oedema, hyperhydratation and decompensated cardiac insufficiency.
- CLINIMIX® without electrolytes should not be used in cases of hypokalaemia and hyponatraemia.
- CLINIMIX® containing electrolytes should not be used in patients with hyperkalaemia and hypernatraemia.

4.4 Special warnings and precautions for use

- Special clinical monitoring is required at the beginning of any intravenous infusion. Should any abnormal sign occur, the infusion must be stopped.
- Hypertonic solutions may cause venous irritation if infused into a peripheral vein. The choice of a peripheral or central vein depends on the final osmolarity of the mixture.
- The general accepted limit for peripheral infusion is about 800 mOsm/l but it varies considerably with the age and the general condition of the patient and the characteristics of the peripheral veins.
- Frequent clinical evaluation and laboratory determinations are necessary for correct monitoring during administration. These should include blood glucose, ionogram and kidney and liver function tests.
- The electrolyte requirements of patients receiving the solutions should be carefully determined and monitored especially for the electrolyte-free solutions.
- Glucose intolerance is a common metabolic complication in severely stressed patients. With the infusion of the products, hyperglycaemia, glycosuria, and hyperosmolar syndrome may occur. Blood and urine glucose should be monitored on a routine basis and for diabetics insulin dosage should be adapted, if necessary.
- Fluid balance should be monitored during therapy.
- Care should be taken to avoid circulatory overload particularly in patients with cardiac insufficiency and/or failure.
- In patients with hepatic insufficiency, apart from routine liver function tests, possible symptoms of hyperammonaemia should be controlled.
- Solutions containing electrolytes must be infused with caution in patients with abnormally high serum levels of these elements, especially in patients with impaired renal function.
- If the infusion is not continuous over 24 hours, keep to an appropriate infusion rate; possibly with a gradual increase in the first hour and a gradual decrease in the last hour to avoid abnormal glycaemic peaks.
- In case of severe kidney failure, specially formulated amino acid solutions should be preferred.
- Vitamins and trace elements should be provided to patients receiving parenteral nutrition for a long period.

4.5 Interaction with other medicinal products and other forms of interaction

Not applicable.

4.6 Pregnancy and lactation

The safety of CLINIMIX® in pregnancy and lactation has not been proven due to the lack of clinical studies. The prescriber should consider the benefit/risk relationship in order to administer CLINIMIX® to pregnant or breast-feeding women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The effects which may occur and which require the treatment to be discontinued are as follows: nausea, vomiting and shivering.
These potential undesirable effects may occur as a result of inappropriate use: for example, overdose, excessively fast infusion rate (see sections 4.4 Special warnings and special precautions for use, and 4.9 Overdosage)

Glucose intolerance is a common metabolic complication in severely stressed patients. With the infusion of the products, hyperglycaemia, glycosuria, and hyperosmolar syndrome may occur.

4.9 Overdose

In cases of incorrect administration (dosage and rate), signs of hypervolemia and acidosis may be observed. Hyperglycemia, glycosuria, and a hyperosmolar syndrome may occur with excessive glucose infusion. A too rapid infusion of amino acid may result in nausea, vomiting and shivering. In such cases, discontinue the infusion immediately.

In some serious cases, haemodialysis, haemofiltration or haemo-dia-filtration may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parental nutrition / mixtures
ATC code: B05 BA 10

As a parenteral nutrition intravenous fluid, CLINIMIX® injections provide nutritional support to maintain the complex nitrogen-energy balance which may be altered by nutritional depletion and trauma. CLINIMIX® solutions provide a biologically available source of nitrogen (L-amino acids), carbohydrates (as glucose) and electrolytes.

5.2 Pharmacokinetic properties

The amino acids, electrolytes and glucose of CLINIMIX® are distributed, metabolised and excreted in an identical manner typical to the separate amino acids, glucose and electrolytes intravenous solutions.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Amino acids solution:
Acetic acid
Water for injections

Glucose solution:
Hydrochloric acid
Water for injections

6.2 Incompatibilities

Additives may be incompatible, refer to the manufacturer for further details.
If additives are necessary, compatibilities should be checked and the stability of mixtures should be controlled.
The solution should not be administered with, before, or after an administration of blood through the same equipment because of the possibility of pseudoagglutination.

6.3 Shelf Life

- For the dual bags in their overpouch, the shelf life is 2 years.

- *After the peel seal activation, chemical and physical in-use stability has been demonstrated for 7 days at 2 to 8° C followed by 48 hours* below 25°C**.**

- When additions have been made, from a microbiological point of view, the admixture should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless additions have been made under controlled and validated aseptic conditions. If longer storage periods are required in exceptional circumstances, the company can be contacted as chemical and physical in-use stability data for 7 days at 2-8°C followed by 48 hours below 25°C are available for the products listed in section 6.6.d.

6.4 Special precautions for storage

Do not freeze.

For the product supplied in the clear overpouch, keep container in the outer carton.

6.5 Nature and contents of container

CLINIMIX® N12G20E is packaged in a dual compartment plastic bag containing respectively an amino acid solution with electrolytes and a glucose solution with calcium.

The dual container is a multilayer plastic bag packaged in an oxygen barrier overpouch. The overpouch may either be an aluminised plastic laminate or a clear plastic laminate one with an oxygen-absorbing sachet. The sachet must be discarded after removal of the overpouch. The bag material is a multilayer plastic film, of which the inside layer is EVA (ethylvinyl acetate). The bag will be presented in one of two designs, horizontal peel seal and vertical peel seal (see Figures 2 and 4 respectively). The placement of bag ports is dependant upon the design. See Figures 2 and 4. The multilayer plastic is compatible with lipids.

Both compartments are separated by a peel seal. Just before administration, the contents of both chambers are mixed by squeezing or rolling the compartments to break the seal.

3 different formats are available:
1 litre Package size: 8
1.5 litres Package size: 6
2 litres Package size: 4

The compartments volumes are the following:

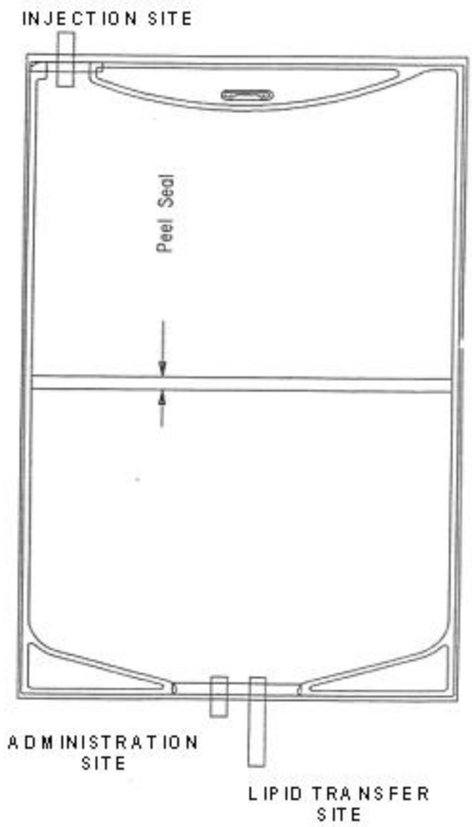
	Bag size		
Compartments	1l	1.5l	2l
Amino acids solution	500 ml	750 ml	1000 ml
Glucose solution	500 ml	750 ml	1000 ml

Not all pack sizes may be marketed
Figure 1

Squeezing of the horizontal CLINIMIX®

Figure 2

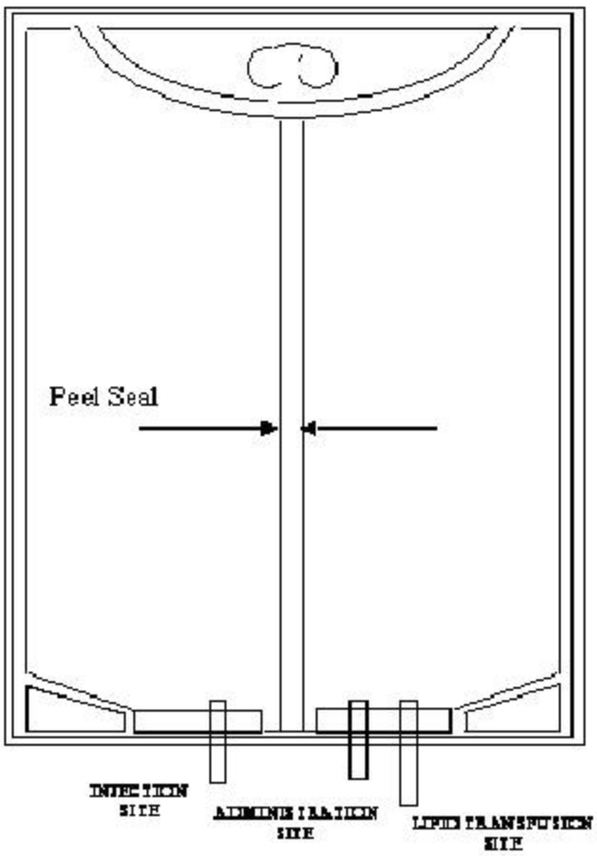
DRAWING OF THE HORIZONTAL PEEL SEAL DUAL BAG



Squeezing or rolling of the vertical CLINIMIX®

Figure 4

DRAWING OF THE VERTICAL PEEL SEAL DUAL BAG



6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

- Do not use unless solution is clear and container undamaged.
- CLINIMIX® activation can be performed in the overpouch or after its removal. Administer the product only after breaking the seal and mixing the contents of both compartments.
- For single use only. Do not store partly used containers and discard all equipment after use. Do not reconnect partially used bag. Do not connect in series in order to avoid air embolism due to possible residual air contained in the primary bag.
- As with all parenteral solutions, compatibility should be checked when additives are used. Thorough and careful aseptic mixing of any additives is mandatory.

CLINIMIX® solutions are presented in two different bags designs, see Section 6.5 for details. The direction for use hereafter applies for both designs.

a. <u>To open the overpouch</u>

- Use slits at each side to tear overwrap.

b. To mix solutions

- Ensure that the product is at room temperature.
- Grasp the container firmly on each side of the top of the bag.
- Squeeze to activate. (see figure 1 or 3). Product supplied with the vertical peel-seal design may also be activated by rolling (see Figure 3).
- Mix by inverting the bag 2 or 3 times.

c. Preparation for administration

- Suspend the container.
- Remove the protective cover from the administration port site (the smaller port of the pair of the ports of the container, see figure 2 or 4).
- Firmly insert the administration set spike into the administration port.

d. Addition to CLINIMIX® (see section 6.2. also)

Warning: The supplementation can be made, either before activation of the container in the dextrose solution for vitamins only, or after opening the peel seals (once the two solutions have been mixed) for all additives. *CLINIMIX® may be supplemented with:*

- *Lipid emulsions (for example ClinOleic®) at a rate of 50 to 250 ml per litre of CLINIMIX®*

	CLINIMIX® N12G20E 1 l + 100 ml lipids 20%*	CLINIMIX® N12G20E 1.5 l + 250 ml lipids 20%*	CLINIMIX® N12G20E 2 l + 250 ml lipids 20% *
Nitrogen (g) Amino acids (g) Glucose (g) Lipid (g)	5.8 35 100 20	8.7 53 150 50	11.6 70 200 50
Total calories (kcal) Glucose calories (kcal) Lipid calories (kcal) Glucose/lipids Ratio	740 400 200 67/33	1310 600 500 55/45	1580 800 500 62/38
Sodium (mmol) Potassium (mmol) Magnesium (mmol) Calcium (mmol) Acetate (mmol) Chloride (mmol) Phosphate as HPO_4^{--} (mmol)	35 30 2.5 2.3 60 30 15	53 45 3.8 3.4 90 60 23	70 60 5.0 4.5 120 80 30
pH Osmolarity (mOsm/l)	6 990	6 950	6 975

Electrolytes: per litre of Clinimix®

	Sodium	Potassium	Magnesium	Calcium
Up to a final concentration of	80 mmol	60 mmol	5.6 mmol	3.0 mmol

Trace elements: per litre of Clinimix®

Up to a final concentration of	**Copper**	10 µmol	Zinc	77 µmol
	Chromium	0.14 µmol	Manganese	2.5 µmol
	Fluorine	38 µmol	Cobalt	0.0125 µmol
	Selenium	0.44 µmol	Molybdenum	0.13 µmol
	Iodine	0.5 µmol	Iron	10 µmol

Vitamins: per litre of Clinimix®

Up to a final concentration of	**vitamin A**	1750 IU	Biotin	35 µg
	vitamin B6	2.27 mg	vitamin B1	1.76 mg
	vitamin D	110 IU	Folic acid	207 µg
	vitamin B12	3.0 µg	vitamin B2	2.07 mg
	vitamin E	5.1 mg	vitamin C	63 mg
	vitamin PP	23 mg	vitamin B5	8.63 mg
	vitamin K	75 µg		

Stability data for supplementation of CLINIMIX® with other marketed lipid emulsions and other additives or nutrients c available upon request.

If some light creaming is observed, mix thoroughly the admixture by gentle agitation to get a uniform emulsion before t infusion.

Additions should be performed under aseptic conditions.
Additions can be made with a syringe or a transfer set.

- Addition with a syringe or a transfer set fitted with a needle

Prepare the injection site (the single port, see figure 2 or 4).
Puncture the port and inject.
Mix the solutions and the additives.

- Addition with a transfer set fitted with a spike

Please refer to the “Directions for use” of the lipid transfer set used.
Connect the spike to the transfusion site (the longest port).

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA 0167/098/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 30 April 1996
Date of last renewal: 12 December 2004

10 DATE OF REVISION OF THE TEXT

September 2005