A QUIEN CORRESPONDA

DECLARACIÓN DE COMPATIBILIDAD

D. ALFONS VILLAGRASA BOT, como Director Técnico Farmacéutico de la empresa **FRESENIUS KABI ESPAÑA, S.A.U.,** con domicilio social en Barcelona (08005), calle Marina 16-18,

DECLARA

Que en relación a los siguientes productos, comercializados por Fresenius Kabi España,

PLAST-APYR FISIOLÓGICO (250 ml, 500 ml)

PLAST-APYR GLUCOSADO 5% (50 ml, 100 ml, 250 ml, 500 ml)

PLAST-APYR GLUCOSALINO (500 ml)

Que el material de acondicionamiento utilizado en la fabricación de los componentes del frasco Plast-Apyr es polietileno de baja densidad y cumple la monografía de la Farmacopea Europea 3.1.4 "Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations". Este material es apto para uso farmacéutico y no representa ningún riesgo toxicológico.

El tapón es del mismo tipo de polietileno, con una lámina de caucho natural. El material del tapón cumple con la monografía de farmacopea 3.1.4 "Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations". El material de la lámina (stopper) cumple con la monografía de farmacopea 3.2.9."Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders". Estos materiales son aptos para uso farmacéutico y no representan ningún riesgo toxicológico.

Se han realizado estudios de migración con otros envases de polietileno (ampollas y frascos Kabipac), que son totalmente extrapolables, que demuestran la idoneidad del envase. Por lo que respecta a los estudios de adsorción, quedan cubiertos con los estudios de estabilidad (determinación del contenido de los ingredientes). En todos los estudios de estabilidad realizados, no hay evidencias de que los principios activos utilizados en las soluciones de infusión interactúen con el polietileno.

En base a todo lo anterior, declaramos que estos materiales son adecuados para ser utilizados como material de acondicionamiento de frascos de infusión de cloruro sódico, glucosa al 5% o solución glucosalina. El frasco de polietietileno puede ser esterilizado sin que se produzcan alteraciones, como fisuras o coloración. Se ha establecido la integridad del envase, ya que durante el proceso se comprueba en todas las unidades mediante el test de integridad.

La idoneidad de los frascos de polietileno Plast-Apyr ha sido demostrada mediante controles físico-químicos, mecánicos y biológicos. Dichos estudios, junto con los datos de estabilidad del producto acabado,

demuestran la idoneidad de los frascos de polietileno Plast-Apyr como acondicionamiento primario de soluciones de infusión de cloruro sódico, glucosa al 5% o solución glucosalina.

Por lo que respecta al impacto de otros fármacos que puedan ser adicionados a las soluciones de infusión, se dispone de los datos de compatibilidad de Cloruro Sódico con otros fármacos (Trissel, 15th edición).

Se adjunta a la presente declaración:

- **Declaraciones de conformidad relativa al cumplimiento del polietileno de baja densidad respecto a la monografía de la Farmacopea Europea.**
- **Compatibilidad del Cloruro Sódico: "Sodium Chloride, Handbook on Injectable Drugs, L.A. Trissel, 15th edition, p. 1441-1443".**

Y para que conste a los efectos oportunos, firmo la presente en Barcelona, a 8 de marzo de 2013.

Fdo. Alfons Villagrasa Bot
Director Técnico Farmacéutico

Declaración de Conformidad

Fresenius Kabi confirma que el polietileno de baja densidad (LDPE) utilizado para la producción de los frascos de Plast-Apyr cumple con los requerimientos establecidos en la Farmacopea Europea, edición vigente

Monograph 3.1.4 "Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations".

Y para que conste a los efectos oportunos, firmo la presente en Barcelona, a 8 de marzo de 2013.

Fdo. Alfons Villagrasa Bot
Director Técnico Farmacéutico

Alkali-Labile Drugs — Drugs such as sodium bicarbonate that may raise the pH of an admixture above 6 may cause significant decomposition of isoproterenol hydrochloride and norepinephrine bitartrate. If they are combined, the mixture should be administered immediately after preparation. (59; 77) Also, dopamine hydrochloride is inactivated in alkaline solutions such as sodium bicarbonate 5%. (79)

Amiodarone Hydrochloride — The manufacturer of amiodarone hydrochloride states that the drug may precipitate if mixed with sodium bicarbonate. (1-3/06)

Calcium Salts — The manufacturer recommends avoiding the addition of sodium bicarbonate to infusion solutions that contain calcium unless compatibility has been established. Haze formation or precipitation may result from such combinations. (4)

Sodium bicarbonate (Abbott) in dextrose 5% has been reported to be conditionally compatible with calcium chloride (Upjohn) and calcium gluconate (Upjohn). The incompatibility is dependent on the concentration of the additives. Therefore, if attempting to combine sodium bicarbonate with either of these drugs, mix the solution thoroughly and observe it closely for any sign of incompatibility. (15) A white precipitate and turbidity were found in concentrated solutions. (845)

Cefotaxime — Cefotaxime should not be mixed in alkaline solutions such as sodium bicarbonate injection. (4)

Ciprofloxacin — Ciprofloxacin mixed with sodium bicarbonate in lower concentrations has resulted in the formation of a haze and precipitate, while 10-fold higher concentrations of sodium bicarbonate appear to be physically compatible with the same amount of ciprofloxacin. (1869) Although not unprecedented, it is less common for high concentrations of drugs to be compatible while lower concentrations are incompatible. The differing compatibility results have been ascribed to pH dependency of ciprofloxacin solubility. (2012) However, a thorough evaluation of the compatibility of ciprofloxacin with a wide range of sodium bicarbonate concentrations found that incompatibility cannot be predicted by pH of the solutions alone; the solutions were generally in a very narrow pH range (8.0 to 8.3). Because the interaction between ciprofloxacin and sodium bicarbonate appears to be complex and variable, simultaneous administration of these drugs should be avoided. (2065)

Dobutamine Hydrochloride — Dobutamine hydrochloride has been stated to be incompatible with alkaline solutions and should not be mixed with sodium bicarbonate 5% or other alkaline solutions. (4)

Methylprednisolone — The compatibility of methylprednisolone sodium succinate (Upjohn) with sodium bicarbonate added to an auxiliary medication infusion unit has been studied. Primary admixtures were prepared by adding sodium bicarbonate 44.6 mEq/L to dextrose 5%, dextrose 5% in sodium chloride 0.9%, and Ringer's injection, lactated. Up to 100 mL of the primary admixture was added along with methylprednisolone sodium succinate (Upjohn) to the auxiliary medication infusion unit with the following results (329):

Methylprednisolone Sodium Succinate	Sodium Bicarbonate 44.6 mEq/L Primary Solution	Results
500 mg	D5S, D5W qs 100 mL	Clear solution for 24 hr
500 mg	LR qs 100 mL or added to 100 mL LR	Clear solution for 1 hr
1000 mg	D5W qs 100 mL	Clear solution for 24 hr
1000 mg	D5S qs 100 mL or added to 100 mL D5S	Clear solution for 24 hr
1000 mg	LR qs 100 mL	Clear solution for 1 hr
1000 mg	Added to 100 mL LR	Clear solution for 4 hr
2000 mg	D5S, D5W qs 100 mL	Clear solution for 24 hr
2000 mg	LR qs 100 mL	Clear solution for 30 min
2000 mg	Added to 100 mL LR	Clear solution for 4 hr

Other Drugs — Sodium bicarbonate is stated to be incompatible with acids, acidic salts, and many alkaloidal salts. (4)

Ticarcillin disodium–clavulanate potassium is stated to be incompatible with sodium bicarbonate. (4)

SODIUM CHLORIDE
AHFS 40:12

Products — Sodium chloride additive solution is available in various size containers in concentrations of 14.6 and 23.4%. The 14.6% concentration contains sodium chloride 146 mg/mL and provides 2.5 mEq/mL of sodium and chloride ions. The 23.4% concentration contains sodium chloride 234 mg/mL and provides 4 mEq/mL of sodium and chloride ions. (1-2/06; 29)

NOTE: Do not confuse these high concentration additive solutions with other sodium chloride products with lower concentrations.

Sodium chloride 0.45 and 0.9% infusion solutions are available in a variety of sizes from 25 to 1000 mL. The 0.45 and 0.9% concentrations provide 77 and 154 mEq of sodium and chloride per liter, respectively. (1-2/06; 4; 29)

pH — From 4.5 to 7. (17)

Osmolarity — Sodium chloride additive solutions are very hypertonic and must be diluted for use. The osmolarities of the 14.6 and 23.4% concentrations have been calculated to be about 5000 and 8000 mOsm/L, respectively. (4) The osmolality of the 14.6% concentration

was determined to be 5370 mOsm/kg by freezing-point depression and 4783 mOsm/kg by vapor pressure. (1071) A 0.9% sodium chloride solution is isotonic, having an osmolarity of 308 mOsm/L. A 0.45% sodium chloride solution is hypotonic, having a calculated osmolarity of 154 mOsm/L. (4)

Administration — Sodium chloride additive solutions of 14.6 and 23.4% are administered by intravenous infusion only after dilution in a larger volume of fluid. (4) Dextrose 5% has been recommended for this dilution. (1-2/06) When concentrations of 3 or 5% are indicated, these hypertonic solutions should be administered into a large vein, at a rate not exceeding 100 mL/hr. Infiltration should be avoided. (4)

Stability — Sodium chloride additive solution should be stored at controlled room temperature and protected from excessive heat and freezing. (1-2/06; 17)

Elastomeric Reservoir Pumps — Sodium chloride 0.9% (Baxter) 250 mL was filled into Intermate LV 250 (Baxter) elastomeric infusion devices and stored at 5 and 23 °C for 90 days. The solution remained visually compatible with no change in pH and sodium or chloride concentration and less than 0.1% water loss. (1993)

Compatibility Information

Solution Compatibility

Sodium chloride

Solution	*Mfr*	*Mfr*	*Conc/L*	*Remarks*	*Ref*	*Cll*
Dextran 6% in dextrose 5%	AB	AB	200 mEq	Physically compatible	3	C
Dextran 6% in sodium chloride 0.9%	AB	AB	200 mEq	Physically compatible	3	C
Dextrose–Ringer's injection combinations	AB	AB	200 mEq	Physically compatible	3	C
Dextrose–Ringer's injection, lactated, combinations	AB	AB	200 mEq	Physically compatible	3	C
Dextrose–saline combinations	AB	AB	200 mEq	Physically compatible	3	C
Dextrose 2.5%	AB	AB	200 mEq	Physically compatible	3	C
Dextrose 5%	AB	AB	200 mEq	Physically compatible	3	C
Dextrose 10%	AB	AB	200 mEq	Physically compatible	3	C
Fat emulsion 10%, intravenous	CU		200 mEq	Globule coalescence with noticeable surface creaming in 4 hr at room temperature. Oil globules noted on surface at 48 hr	656	I
	CU		100 mEq	No significant change in emulsion for 24 hr at room temperature. Significant emulsion globule coalescence noted at 48 hr	656	C
Fructose 10% in sodium chloride 0.9%	AB	AB	200 mEq	Physically compatible	3	C
Fructose 10%	AB	AB	200 mEq	Physically compatible	3	C
Invert sugar 5 and 10% in sodium chloride 0.9%	AB	AB	200 mEq	Physically compatible	3	C
Invert sugar 5 and 10%	AB	AB	200 mEq	Physically compatible	3	C
Ionosol products	AB	AB	200 mEq	Physically compatible	3	C
Ringer's injection	AB	AB	200 mEq	Physically compatible	3	C

Solution Compatibility (Cont.)

Sodium chloride

Solution	*Mfr*	*Mfr*	*Conc/L*	*Remarks*	*Ref*	*C/I*
Ringer's injection, lactated	AB	AB	200 mEq	Physically compatible	3	C
Sodium chloride 0.45%	AB	AB	200 mEq	Physically compatible	3	C
Sodium chloride 0.9%	AB	AB	200 mEq	Physically compatible	3	C
Sodium lactate ⅙ M	AB	AB	200 mEq	Physically compatible	3	C

Additive Compatibility

Sodium chloride

Drug	*Mfr*	*Conc/L*	*Mfr*	*Conc/L*	*Test Soln*	*Remarks*	*Ref*	*C/I*
Potassium chloride	LI	80 mEq	BA	3%		Physically compatible for 24 hr	315	C

Drugs in Syringe Compatibility

Sodium chloride

Drug (in syringe)	*Mfr*	*Amt*	*Mfr*	*Amt*	*Remarks*	*Ref*	*C/I*
Cimetidine HCl	SKF	300 mg/2 mL		12.5 mEq/5 mL	Precipitate forms between 36 and 48 hr at room temperature	516	C

Y-Site Injection Compatibility (1:1 Mixture)

Sodium chloride

Drug	*Mfr*	*Conc*	*Mfr*	*Conc*	*Remarks*	*Ref*	*C/I*
Ciprofloxacin	MI	2 mg/mL[a]	AMR	4 mEq/mL	Visually compatible for 2 hr at 25 °C	1628	C

[a]*Tested in dextrose 5%.*

Additional Compatibility Information

Mannitol — The addition of sodium chloride to mannitol 20 or 25% may cause precipitation of the mannitol. (4)