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PHARMACEUTICAL TECHNOLOGY

PHYSICOCHEMICAL AND MICROBIOLOGICAL PROPERTIES OF EYE DROPS CONTAINING CEFUROXIME

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Abstract: The purpose of the studies was to examine the influence of the additives and storage temperature on physicochemical properties and on the antimicrobial activity of cefuroxime in the eye drops. The eye drops were 1% sterile aqueous solutions of cefuroxime in citrate buffer of pH 6.15-6.20, preserved with 0.002% thiomersal or 0.001% phenylmercuric borate with 0.4% β-phenylethyl alcohol. Viscosity of the eye drops was increased using polyvinyl alcohol. The drops, protected from light, were stored at the temperature of 4°C and 20°C. As the criteria of the qualitative assessment of freshly prepared eye drops and during their storage, the following properties were considered: organoleptic analysis (color, clarity, and smell), sterility, pH, osmotic pressure, density, and viscosity, antimicrobial activity of cefuroxime and preservation efficiency of thiomersal and phenylmercuric borate in the eye drops. The storage temperature had a significant influence on the antimicrobial activity of the antibiotic in the eye drops. The antimicrobial activity of cefuroxime in the drops stored for 30 days at the temperature of 4°C did not decrease. Thiomersal at the concentration over 0.003%, 0.005% benzalkonium chloride and 0.01% chlorhexidine diacetate were not compatible with cefuroxime in the drops.

Keywords: cefuroxime in the eye drops, the eye, pharmaceutical interactions of cefuroxime

Cefuroxime (Biofuroksym, Zinacef) is a cephalosporin of second generation characterized by a wide range of antibacterial activity. It is resistant to staphylococcal β-lactamases and to the enzymes of TEM and SHV type, produced by Gram-negative bacteria and cocci. It is efficient against *Staphylococcus* spp., *Streptococcus* spp., *Haemophilus influenzae*, most of *Enterobacteriaceae, Neisseria* spp. and *Moraxella catarrhalis*. Cefuroxime is characterized by the antimicrobial activity towards most of the inflammation-inducing bacteria (1). It is used in the form of 1-5% eye drops or injections, e.g. intracameral injections, in the treatment and protection against intraocular and periocular inflammations (2).

Cefuroxime permeates well from conjunctival sac into aqueous humor and it is less toxic for the epithelium of the cornea in comparison with other topically used antibiotics e.g. gentamicin (3). There are no commercial forms of eye drops containing cefuroxime available for sale. When necessary, they are prepared *ex tempore* by hospital pharmacies for the patients of ophthalmic wards. Those drops are prepared under aseptic conditions usually by the dissolution of cefuroxime in sterile water. They do not contain any preservatives, therefore, if stored at the temperature of 2-8°C, they can be used not later than during 24 hours after their preparation.

Commercial preparations of „artificial tears" were used as a solvent for the preparation of the drops containing cefuroxime (4, 5). The drops which were prepared using „artificial tears" containing benzalkonium chloride did not meet qualitative requirements because of the sediment, which appeared in the drops as a result of the pharmaceutical interaction between benzalkonium chloride and cefuroxime (4).

„Artificial tears" of alkaline pH 8-9 were not suitable solvents for cefuroxime in the eye drops as this pH caused fast degradation of the antibiotic (4). Phenylmercuric acetate did not work as a preservative of the eye drops containing cefuroxime or ceftazidime, either. As a result of the pharmaceutical interaction, phenylmercuric acetate in the presence of both antibiotics degraded losing its antimicrobial properties (6).

The stability of cefuroxime in aqueous solutions is influenced by pH, the presence of additives and particularly by the storage conditions such as the temperature and protection from light. Optimal pH for the stability of this antibiotic is in the range of 4.5-7.3 (7).

The purpose of the studies was to examine the influence of the additives and storage temperature (4°C and 20°C) on the physicochemical properties and on the antimicrobial activity of cefuroxime in the eye drops.

EXPERIMENTAL

Materials

Biofuroksym® (Cefuroximum natricum), IBA Bioton, a 1.5 g, dry substance for intramuscular and intravenous injections; eye drops containing cefuroxime, prepared under aseptic conditions according to the pharmaceutical composition shown in Table 1; sterile solutions of: cefuroxime, citrate buffers, polyvinyl alcohol, preservatives: benzalkonium chloride, thiomersal, phenylmercuric borate and chlorhexidine diacetate.

Reagents

Citric acid monohydrate, sodium citrate p.a., P.P.H. POCH Gliwice, polyvinyl alcohol 72000 (PVA), P.P.H. POCH Gliwice, Thiomersal BP 1998 – Caesar & Lorentz GmbH, phenylmercuric borate Pharma Cosmetic s.c. Cracow, chlorhexidine diacetate monohydrate – Fluka Biochemika, benzalkonium chloride NF, β-phenylethyl alcohol (2-phenylethanol) Merck – Schuchard.

Apparatus

pH-meter (CyberScan 500, Singapore); osmometer (Trident 800cl, Warsaw); Höppler viscosimeter KF10 (Prüfgeräte–Werk, Medingen, Dresden); apparatus for membrane filtration – Sartorius; air sterilizer type S.P.W. 65M (Spółdzielnia Pracy Marki); autoclave EIMI type ESS – 105 (Spółdzielnia Pracy Mechaników, Warsaw); densitometer (Mettler Toledo DA – 110M); electronic analytical scales: up to 0.1 mg – type WPS 36/S and up to 0.002 g type WPS 720/C (Radwag, Radom).

Methods

Preparation of sterile solutions of additives

Citrate buffers I and II, solution of polyvinyl alcohol (PVA), 0.5% solution of benzalkonium chloride, 2% solution of thiomersal, 0.04% solution of phenylmercuric borate and 1% solution of chlorhexidine diacetate. The solutions of additives were prepared and examined using methods mentioned in other publication (8).

Studies of pharmaceutical compatibility of cefuroxime with selected additives used in the technology of the eye drops

Under sterile conditions, the following solutions of additives were added separately into 1% aqueous solutions of cefuroxime: sodium chloride (0.9%), sodium citrate (6%), citric acid (0.3%), HEC (0.25%), HPMC (0.5%), PVA (4%), thiomersal (0.002%), phenylmercuric borate (0.001%), β-phenylethyl alcohol (0.4%), sodium pyrosulfite (0.01%), disodium EDTA (0.03%). The

Table 1. Formulary composition (in grams) of the eye drops containing cefuroxime.

Constituents (per 100 g of the eye drops)	Formulary versions							
	I	II		III	IV		V	VI
		1	2		1	2		
Cefuroxime	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Citrate buffer I Constituents of the buffer: Sodium citrate 3.0 Citric acid 0.15 Water for injections 96.85	99.0	99.0	99.0	-	-	-	99.0	-
Citrate buffer II Constituents of the buffer: Sodium citrate 6.0 Citric acid 0.30 Water for injections 93.70	-	-	-	49.5	49.5	49.5	-	49.5
Solution of polyvinyl alcohol (PVA) viscosity η = 17.11 mPa·s	-	-	-	49.5	49.5	49.5	-	49.5
Thiomersal	-	0.002	0.02	-	0.002	0.02	-	-
Phenylmercuric borate	-	-	-	-	-	-	0.001	0.001
β-phenylethyl alcohol	-	0.4	0.4	-	0.4	0.4	0.4	0.4

Table 2. pH, osmotic pressure and viscosity of the eye drops containing cefuroxime, freshly prepared and stored at the temperature of 4°C and 20°C.

Formulary version	pH							Osmotic pressure (mOsm/L)							Viscosity (mPa·s) drops after preparation and after 30 days of storage (4°C and 20°C)
	Freshly prepared drops	10th day		20th day		30th day		Freshly prepared drops	10th day		20th day		30th day		
		4°C	20°C	4°C	20°C	4°C	20°C		4°C	20°C	4°C	20°C	4°C	20°C	
I	6.20 ± 0.01	6.20 ± 0.01	6.45 ± 0.01	6.26 ± 0.01	6.73 ± 0.01	6.33 ± 0.02	7.20 ± 0.01	336.67 ± 3.21	336.67 ± 3.21	334.67 ± 3.01	333.67 ± 4.73	331.00 ± 4.58	331.67 ± 2.08	321.67 ± 2.52	1.08 ± 0.01
II.1.	6.17 ± 0.02	6.20 ± 0.01	6.47 ± 0.01	6.26 ± 0.01	6.79 ± 0.01	6.33 ± 0.02	7.23 ± 0.01	384.33 ± 4.93	390.33 ± 2.08	367.00 ± 2.64	332.67 ± 4.16	357.67 ± 4.53	319.33 ± 2.08	341.00 ±1.73	1.10 ± 0.02
III	6.19 ± 0.01	6.19 ± 0.01	6.44 ± 0.02	6.22 ± 0.02	6.62 ± 0.01	6.28 ± 0.01	7.10 ± 0.01	378.67 ± 2.08	379.67 ± 6.35	379.67 ± 3.78	373.67 ± 7.64	358.33 ± 1.53	370.00 ± 2.00	364.67 ± 5.77	8.63 ± 0.22
IV.1.	6.18 ± 0.01	6.19 ± 0.01	6.47 ± 0.02	6.29 ± 0.01	6.81 ± 0.01	6.35 ± 0.02	7.36 ± 0.01	390.00 ± 6.24	389.67 ± 1.53	365.67 ± 4.04	356.00 ± 4.36	339.33 ± 6.66	306.67 ± 2.52	310.33 ± 2.08	8.59 ± 0.19
V	6.17 ± 0.01	6.20 ± 0.01	6.47 ± 0.01	6.27 ± 0.01	6.58 ± 0.01	6.26 ± 0.02	6.93 ± 0.02	378.00 ± 3.06	381.00 ± 2.64	377.60 ± 2.52	372.33 ± 3.51	362.00 ± 1.73	359.99 ± 5.00	354.33 ± 2.90	1.09 ± 0.02
VI	6.15 ± 0.02	6.20 ± 0.02	6.41 ± 0.01	6.27 ± 0.01	6.56 ± 0.01	6.26 ± 0.01	6.90 ± 0.01	398.67 ± 2.84	399.33 ± 3.21	407.00 ± 3.01	392.33 ± 3.58	397.33 ± 4.73	383.33 ± 1.53	379.67 ± 3.59	8.64 ± 0.28

Table 3. The results of the studies of antimicrobial activity of cefuroxime in the freshly prepared drops and in those stored at the temperature of 4°C and 20°C in comparison with the standard substance (%).

Formulary versions	Antimicrobial activity of cefuroxime in the eye drops determined using the test strain *Staphylococcus aureus* ATCC 6538P (%) in comparison with the standard substance										
	Storage time (days)										
	Drops after preparation	10		14		18		20		30	
		4°C	20°C	4°C	20°C	4°C	20°C	4°C	20°C	4°C	20°C
I	100.00 ± 0.18	100.00 ± 0.18	100.00 ± 0.18	100.00 ± 0.18	99.63 ± 0.36	100.00 ± 0.18	89.09 ± 0.36	100.00 ± 0.18	84.72 ± 0.43	99.63 ± 0.36	83.63 ± 0.18
II.1.	100.00 ± 0.18	100.00 ± 0.18	99.63 ± 0.36	100.00 ± 0.18	99.63 ± 0.36	100.00 ± 0.18	89.09 ± 0.36	100.00 ± 0.18	84.00 ± 0.36	99.63 ± 0.36	82.90 ± 0.36
III	100.00 ± 0.00	100.00 ± 0.18	100.00 ± 0.18	100.00 ± 0.18	99.63 ± 0.36	100.00 ± 0.18	89.09 ± 0.36	100.00 ± 0.18	84.36 ± 0.36	99.63 ± 0.18	83.27 ± 0.36
IV.1.	100.00 ± 0.18	100.00 ± 0.18	99.63 ± 0.36	100.00 ± 0.18	99.63 ± 0.36	100.00 ± 0.18	89.09 ± 0.36	100.00 ± 0.18	84.36 ± 0.36	100.00 ± 0.18	83.27 ± 0.36
V	100.00 ± 0.18	100.00 ± 0.18	99.63 ± 0.18	100.00 ± 0.18	99.63 ± 0.18	100.00 ± 0.18	89.09 ± 0.36	100.00 ± 0.18	83.63 ± 0.43	99.63 ± 0.18	82.90 ± 0.44
VI	99.93 ± 0.18	100.00 ± 0.18	99.63 ± 0.18	100.00 ± 0.18	99.63 ± 0.18	100.00 ± 0.18	89.09 ± 0.36	100.00 ± 0.18	84.00 ± 0.43	99.63 ± 0.18	83.27 ± 0.44

Table 4. Statistical evaluation of the results of physicochemical studies and antimicrobial activity of cefuroxime in the eye drops.

Parameters of statistical evaluation	pH	Osmotic pressure (mOsm/L)	Viscosity (mPa·s)	Antimicrobial activity of cefuroxime in the drops in comparison with the standard	
				Standard cefuroxime solution	Freshly prepared eye drops
$\overline{X}$	6.15	398.67	8.64	27.52 mm	27.50 mm
s	0.012583	1.788895	0.1766352	0.0833	0.1968
$S_{\bar{x}}$	0.0062915	0.894447	0.0883176	0.0277	0.0656
μ	6.15 ± 0.02	398.67 ± 2.84	8.64 ± 0.28	27.52 ± 0.06	27.50 ± 0.15
C_v (%)	0.2045	0.4487	2.0443	0.302	0.715
n = 4, f = 3, α = 0.05, $t_{\alpha f}$ = 3.18				n = 9, f = 8, α = 0.05, $t_{\alpha f}$ = 2.306	
Antimicrobial activity of cefuroxime in the drops against the standard				100.00%	99.93%

solutions of cefuroxime containing additives, protected from light, were stored at the temperature of 4°C and 20°C for 14 days and were examined for their color and clarity.

Preparation of the eye drops containing cefuroxime

Under sterile conditions cefuroxime was dissolved in the recommended volume of citrate buffer I or II (Table 1). After preservation, the solution was filtered through membrane filter with pore diameter 0.22 μm (Sartorius). The viscosity of the filtered eye drops was enhanced with the solution of PVA. For the preservation of the eye drops 2% solution of thiomersal or 0.04% solution of phenylmercuric borate were used. The eye drops were stored at the temperature of 4°C and 20°C and protected from light. Qualitative assessment of freshly prepared eye drops and during their storage is presented in Tables 2 and 3. Statistical evaluation of the results is presented in Table 4.

Physicochemical evaluation of the eye drops containing cefuroxime after their preparation and those stored at the temperature of 4°C and 20°C.

Organoleptic analysis

The appearance of the drops: clarity, color and smell were assessed.

pH, osmotic pressure and viscosity

pH of the eye drops was determined with pH-meter, osmotic pressure was assessed with osmometer, viscosity measurements were performed with Höppler viscosimeter. The results of the studies are shown in Table 2, statistical evaluation is presented in Table 4.

Microbiological assessment of the eye drops containing cefuroxime

Sterility studies

Sterility of the eye drops was confirmed with the PPh VI method using membrane filters. After 14 days of incubation on the liquid thioglycolate medium (PB1) and on the medium containing casein and soya hydrolysates (PB2), the bacterial growth was not observed.

Determination of antimicrobial activity of cefuroxime in the eye drops using microbiological method

The antimicrobial activity of cefuroxime in the freshly prepared drops and during their storage at the temperature of 4°C and 20°C was determined using cylinder-plate method, which is described in Polish Pharmacopoeia (PPh) VI. The test strain *Staphylococcus aureus* ATCC 6538P was used.

The results of the studies of the antimicrobial activity of cefuroxime in the eye drops are shown in Table 3, the assessment of the precision of the method is presented in Table 4.

Studies of antimicrobial efficiency of preservatives: thiomersal and phenylmercuric borate in the eye drops containing cefuroxime (preservation assay)

The antimicrobial efficiency of thiomersal and phenylmercuric borate in the drops was examined with the preservation assay according to PPh

Table 5. Degree of cell reductions of test strains *Staphylococcus aureus ATCC 6538, MRSA, Pseudomonas aeruginosa ATCC 9027* in the eye drops containing cefuroxime (preservation assay).

Eye drops containing 1% cefuroxime			Degree of active cells reduction (%) after time (t)											
			Staphylococcus aureus ATCC 6538				*MRSA*				*Pseudomonas aeruginosa ATCC 9027*			
Version no.	Preservatives in the drops	Concentration (%)	CFU/mL	6 h 99.00%*	24 h 99.90%*	28 days 100.00%*	CFU/mL	6 h 99.00%*	24 h 99.90%*	28 days 100.00%*	CFU/mL	6 h 99.00%*	24 h 99.90%*	28 days 100.00%*
II.1.	thiomersal β-phenylethyl alcohol	0.002 0.4	8.6×10^5	99.67	99.90	100.00	8.0×10^5	99.60	99.20	100.00	8.9×10^5	99.64	99.82	100.00
IV.1.	thiomersal β-phenylethyl alcohol (drops of increased viscosity)	0.002 0.4	8.1×10^5	99.79	99.95	100.00	8.8×10^5	99.84	99.39	100.00	8.4×10^5	99.97	99.98	100.00
V	phenylmercuric borate β-phenylethyl alcohol	0.001 0.4	7.4×10^5	99.60	99.99	100.00	8.9×10^5	99.46	99.97	100.00	8.0×10^5	99.97	100.00	100.00
VI	phenylmercuric borate β-phenylethyl alcohol (drops of increased viscosity)	0.001 0.4	7.7×10^5	99.80	99.89	100.00	8.2×10^5	99.62	99.87	100.00	8.2×10^5	99.05	100.00	100.00

*) requirements according to PPh VI

Table 6. Degree of cell reduction of test strains *Bacillus cereus, Listeria monocytogenes, Candida albicans ATCC 10231, Aspergillus niger ATCC 16404* in the eye drops containing cefuroxime (preservation assay).

Eye drops containing 1% cefuroxime			Degree of active cells reduction (%) after time (t)													
			Bacillus cereus				*Listeria monocytogenes*				*Candida albicans ATCC 10231*			*Aspergillus niger ATCC 16404*		
Version no.	preservatives in the drops	Concentration (%)	CFU/mL	6 h 99.00%*	24 h 99.90%*	28 days 100.00%*	CFU/mL	6 h 99.00%*	24 h 99.90%*	28 days 100.00%*	CFU/mL	7 days 99.00%*	28 days **	CFU/mL	7 days 99.00%*	28 days **
II.1.	thiomersal β-phenylethyl alcohol	0.002 0.4	7.1×10^5	99.79	99.76	99.77	7.5×10^5	99.59	99.54	100.00	7.2×10^5	99.99	100.00	7.5×10^5	99.99	100.00
IV.1.	thiomersal β-phenylethyl alcohol (drops of increased viscosity)	0.002 0.4	7.5×10^5	99.89	99.88	99.88	7.1×10^5	99.71	99.71	100.00	7.5×10^5	100.00	100.00	7.5×10^5	99.99	100.00
V	phenylmercuric borate β-phenylethyl alcohol	0.001 0.4	7.2×10^5	99.86	99.82	99.88	8.9×10^5	100.00	100.00	100.00	6.9×10^5	100.00	100.00	6.0×10^5	100.00	100.00
VI	phenylmercuric borate β-phenylethyl alcohol (drops of increased viscosity)	0.001 0.4	7.8×10^5	99.85	99.84	99.87	8.4×10^5	100.00	100.00	100.00	6.1×10^5	100.00	100.00	6.1×10^5	100.00	100.00

*) requirements according to PPh VI

**) – according to PPh VI: after 28 days the number of microorganisms is not expected to increase

VI using test microbial strains mentioned in PPh VI, i.e. *Pseudomonas aeruginosa* ATCC 9027, *Staphylococcus aureus* ATCC 6538, *Candida albicans* ATCC 10231 and *Aspergillus niger* ATCC 16404. Moreover, the bacteria which are dangerous for the eye but were not mentioned in the preservation assay of PPh VI were also taken into account. These were *MRSA* KO1, *Listeria monocytogenes* and *Bacillus cereus* KO2. Additional non-pharmacopoeial test microorganisms, which were included in the studies of antimicrobial efficiency of preservatives in the drops, were clinical strains isolated from the eyes of patients.

The results of the studies are presented in Tables 5 and 6.

RESULTS AND DISCUSSION

The eye drops submitted for analysis were 1% sterile aqueous solutions of cefuroxime in citrate buffer of pH 6.15-6.20, preserved with 0.002% thiomersal or 0.001% phenylmercuric borate mixed with β-phenylethyl alcohol (Table 1). The viscosity of the drops was increased using polyvinyl alcohol. The test of pharmaceutical compatibility showed that among examined additives, the pharmaceutical interaction with 1% solution of cefuroxime was initiated by preservatives such as thiomersal at the concentration over 0.003%, 0.005% benzalkonium chloride and 0.01% chlorhexidine diacetate. The interactions were studied organoleptically on the basis of the loss of clarity or presence of sediment. The eye drops were titrated to pH 6.15-6.20, which is in the range of optimal pH for the stability of cefuroxime i.e. pH 4.5-7.3 (7), and causes no eye irritations.

The influence of the selected constituents of the eye drops on their physicochemical stability and on the antimicrobial activity of cefuroxime in the drops was examined on the basis of the analysis of the drops prepared according to six formulary versions (Table 1). The drops, protected from light, were stored for 30 days at the temperature of 4°C and 20°C. As the criteria of qualitative assessment the following parameters were analyzed: organoleptic properties (color, clarity, smell), sterility, pH, osmotic pressure, density, viscosity, antimicrobial activity of cefuroxime in the drops and the preservation efficiency of thiomersal and phenylmercuric borate mixed with β-phenylethyl alcohol in the drops. During the storage the drops were clear, the color was gradually changing from light to bright yellow. The drops after 30 days of storage at the temperature of 20°C turned bright yellow, while in those stored for 30 days at the temperature of 4°C the change of color was not significant. The change of smell was not observed in drops stored at either temperature. The sediment appeared in the drops of formulary versions II. 2. and IV. 2., which was the consequence of the interaction between cefuroxime and thiomersal. Sediment-containing drops were eliminated from further studies. pH of the drops during their storage was increasing, but the process was taking place much faster in the drops stored at the temperature of 20°C in comparison with the drops stored at the temperature of 4°C. After 20 days of storage at the temperature of 20°C, pH started to grow dynamically from pH 6.15-6.20 to pH 6.90-7.36 (Table 2). This process was strictly related to the decrease in the antimicrobial activity of cefuroxime in the eye drops (Table 3). After 30 days, pH slightly increased (up to pH 6.26-6.35) in the drops stored at the temperature of 4°C. Almost 100% of the initial antimicrobial activity of cefuroxime was retained in the drops of all formulary versions. It shows that the additives used in the drops did not have any influence on the antimicrobial activity of cefuroxime, whereas the activity of cefuroxime in the drops was significantly influenced by their storage temperature. The additives did not have impact on the result of the determination of the antimicrobial activity of cefuroxime in the drops. This is confirmed by the antimicrobial activity of cefuroxime which is very similar to the standard in the freshly prepared drops (Table 4).

Osmotic pressure in the freshly prepared drops was 336.67-398.67 mOsm/L. During their storage it decreased similarly for both storage temperatures (Table 2).

The viscosity of the freshly prepared drops was 1.08-1.10 mPa·s and 8.59-8.64 mPa·s (drops of increased viscosity). After 30 days of storage at both temperatures the viscosity of the drops did not change (Table 2).

The results of the preservation assay showed that 0.002% thiomersal mixed with β-phenylethyl alcohol did not meet the requirements of PPh VI, mentioned in the preservation assay. The cell reduction of test strains *Pseudomonas aeruginosa* ATCC 9027 in the drops of version II. 1. was too low and not compatible with the preservation assay. The cell reduction of *Listeria monocytogenes* in the drops was not sufficient either (Tables 5, 6).

Phenylmercuric borate at the concentration of 0.001% mixed with β-phenylethyl alcohol met the requirements of the preservation assay of PPh VI in relation to the pharmacopoeial test strains. Slightly

worse results were observed in case of cell reduction of *MRSA* and *Bacillus cereus*, whose 100% reduction was not achieved up to the 28th day of the studies (Tables 5, 6).

The results of the studies mentioned above show the opportunity of their application in the pharmaceutical practice in the formulary preparation of the drops and in suggesting the period of storing and using the drops. On the basis of the studies of the antimicrobial activity of cefuroxime in the drops stored at the temperature of 4°C, the following period of their storage can be proposed: for the preserved drops (formulary versions no. V and VI) the storage and application period should be 14 days, while for the drops which were not preserved (formulary versions no. I and III) in unopened packing, the storage period should be 14 days, after the first opening of the packing it should be 24 hours.

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