MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

133 Molesworth Street
PO Box 5013
Wellington 6140
New Zealand
T +64 4 496 2000

26 JUN 2019

[redacted]

Response to your request for official information

Thank you for your request of 4 June 2019 under the Official Information Act 1982 (the Act) for:

> *"I wish to request the following information regarding (the now lapsed medicine) Keflex, granules for oral suspension, cefalexin monohydrate, 25mg/ml and 50mg/ml (File references: TT50- 1566/2, TT50-1566/2a):*
>
> *· Please provide a copy of the most recent datasheet (approved in a CMN or notified in a SACN).*
> *· Please provide a copy of the most recent primary and secondary labelling (approved in a CMN or notified in a SACN)."*

The information held by the Ministry of Health (the Ministry) pertaining to your request is outlined below and copies of these are attached.

Appendix 1	Most recently approved data sheet (dated 1 May 2003)
Appendix 2	Most recently approved primary and secondary labels (dated 1998)

I trust this information fulfils your request. You have the right, under section 28 of the Act, to ask the Ombudsman to review any decisions made under this request.

Please note this response (with your personal details removed) may be published on the Ministry of Health website.

Yours sincerely

Chris James
Group Manager
MedSafe

Data Sheet

KEFLEX

Cephalexin monohydrate, capsules 250 mg, tablets 500 mg, suspension (granules for) 125 mg/5mL and 250 mg/5mL.

Presentation

KEFLEX Capsules 250 mg: green and white capsule Size 2 imprinted "Lilly H69" in black ink on cap and body. Each capsule contains cephalexin monohydrate equivalent to 250 mg cephalexin.
KEFLEX Tablets 500 mg: peach coloured, capsule shaped 16mm by 8mm, upper surface embossed "Lilly ", lower scored and embossed "U49". Each tablet contains cephalexin monohydrate equivalent to 500 mg cephalexin.
KEFLEX Suspension 125 mg/5mL: pink granules yield a deep pink suspension when constituted with water. Each 5mL of suspension contains cephalexin monohydrate equivalent to 125 mg cephalexin.
KEFLEX Suspension 250 mg/5mL: orange granules yield an orange suspension when constituted with water. Each 5mL of suspension contains cephalexin monohydrate equivalent to 250 mg cephalexin.

Uses

Actions

Cephalexin is a semi-synthetic cephalosporin antibiotic intended for oral administration.

Microbiology - *In vitro* tests

In vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephalexin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the 'Indications and Usage' section:
Aerobes, Gram-positive:
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis (penicillin-susceptible strains)
Streptococcus pneumoniae
Streptococcus pyogenes
Aerobes, Gram-negative:
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Proteus mirabilis

Note - Methicillin-resistant staphylococci and most strains of enterococci (*Enterococcus faecalis*) are resistant to cephalosporins including cephalexin. Penicillin-resistant *Streptococcus pneumoniae* is usually cross-resistant to beta-lactam antibiotics. It is not active against most strains of *Enterobacter* spp, *Morganella morganii* and *Proteus vulgaris*. It has no activity against *Pseudomonas* spp or *Acinetobacter calcoaceticus*.

Susceptibility Tests - Diffusion techniques

Quantitative methods that require measurement of zone diameters provide reproducible estimates of susceptibility of bacteria to antimicrobial compounds. One such standardised procedure[1] that has been recommended for use with discs to test the susceptibility of microorganisms to cephalexin uses the 30 mcg cephalothin disc. Interpretation involves correlation of the diameter obtained in the disc test with the minimum inhibitory concentration (MIC) for cephalexin.
Reports from the laboratory providing results of the standard single-disc susceptibility test with a 30 mcg cephalothin disc should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
greater than or equal to 18	(S) Susceptible
15-17	(I) Intermediate
less than or equal to 14	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible medicine, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of medicine can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.
Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections (See 'Pharmacokinetics' section for information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial medicine.)

Standardised susceptibility test procedures require the use of laboratory control microorganisms. The 30 mcg cephalothin disc should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	15-21
S. aureus ATCC 25923	29-37

Dilution techniques

Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardised procedure uses a standardised dilution method[2] (broth, agar, microdilution) or equivalent with cephalothin powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
less than or equal to 8	(S) Susceptible
16	(I) Intermediate
greater than or equal to 32	(R) Resistant

Interpretation should be as stated above for results using diffusion techniques.
As with standard diffusion techniques, dilution methods require the use of laboratory control

microorganisms. Standard cephalothin powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
E. coli ATCC 25922	4-16
E. faecalis ATCC 29212	8-32
S. aureus ATCC 29213	0.12-0.5

Pharmacokinetics

KEFLEX is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 mg, 500 mg, and 1 g, average peak serum levels of approximately 9, 18 and 32 mg/L respectively were obtained at one hour. Measurable levels were present six hours after administration. Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the medicine was excreted unchanged in the urine within 8 hours. During this period, peak urine concentrations following the 250 mg, 500 mg and 1 g doses were approximately 1000, 2200, and 5000 mg/L respectively.

Indications

KEFLEX is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:
Bacterial sinusitis caused by streptococci, *S. pneumoniae*, and *Staphylococcus aureus* (methicillin-sensitive only)
Respiratory tract infections caused by *S. pneumoniae* and *S. pyogenes* (Penicillin is the usual medicine of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cephalexin is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cephalexin in the subsequent prevention of either rheumatic fever or bacterial endocarditis are not available at present.)
Otitis media due to *S. pneumoniae*, *H. influenzae*, staphylococci, streptococci, and *M. catarrhalis*
Skin and skin-structure infections caused by staphylococci and/or streptococci.
Bone infections caused by staphylococci and/or *P. mirabilis*
Genitourinary tract infections, including acute prostatitis, caused by *E. coli*, *P. mirabilis*, and *Klebsiella pneumoniae*
Dental infections caused by staphylococci and/or streptococci.
Note - Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

Dosage and Administration

KEFLEX is administered orally.
Adults - The adult dosage ranges from 1 to 4 g daily in divided doses. The usual adult dose is 250 mg every 6 hours. For the following infections, a dosage of 500 mg may be administered every 12 hours: streptococcal pharyngitis, skin and skin-structure infections, and uncomplicated cystitis in patients over 15 years of age. Cystitis therapy should be continued for 7 to 14 days. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of cephalexin greater than 4 g are required, parenteral cephalosporins, in appropriate doses, should be considered.
Children - The usual recommended daily dosage for children is 25 to 50 mg/kg in divided doses. For streptococcal pharyngitis in patients over 1 year of age, mild, uncomplicated urinary tract infections, and for skin and skin-structure infections, the total daily dose may be divided and administered every 12 hours.

KEFLEX SUSPENSION

Child's Weight	125 mg/5mL	250 mg/5mL
10 kg	2.5 to 5 mL four times a day.	1.25 to 2.5 mL four times a day.
20 kg	5 to 10 mL four times a day.	2.5 to 5 mL four times a day.
40 kg	10 to 20 mL four times a day.	5 to 10 mL four times a day.

or

Child's Weight	125 mg/5mL	250 mg/5mL
10 kg	5 to 10 mL twice a day.	2.5 to 5 mL twice a day.
20 kg	10 to 20 mL twice a day.	5 to 10 mL twice a day.
40 kg	20 to 40 mL twice a day.	10 to 20 mL twice a day.

In severe infections, the dosage may be doubled.
In the therapy of otitis media, clinical studies have shown that a dosage of 75 to 100 mg/kg/day in 4 divided doses is required.

In the treatment of ß-haemolytic streptococcal infections, a therapeutic dosage of cephalexin should be administered for at least 10 days.

Contraindications

KEFLEX is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings and Precautions

Warnings

Before cephalexin therapy is instituted, careful inquiry should be made concerning previous hypersentitivity reactions to cephalosporins and penicillin. Cephalosporin C derivatives should be given cautiously to penicillin-sensitive patients. Serious acute hypersensitivity reactions may require adrenaline and other emergency measures.
There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both medicines. Any patient who has demonstrated some form of allergy, particularly to medicines, should receive antibiotics cautiously. No exception should be made with regard to KEFLEX.
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to medicine discontinuance alone. In moderate to severe cases, appropriate measures should be taken.

Use in Pregnancy

Safe use of this product during pregnancy has not been established. (See 'Precautions' section).

Precautions

General

Patients should be followed carefully so that any side effects or unusual manifestations of medicine idiosyncrasy may be detected. If an allergic reaction to cephalexin occurs, the medicine should be discontinued and the patient treated with the usual agents (e.g. adrenaline or other pressor amines, antihistamines, or corticosteroids).
Prolonged use of cephalexin may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.
KEFLEX should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.
Indicated surgical procedures should be performed in conjunction with antibiotic therapy.
As with other ß-lactams the renal excretion of cephalexin is inhibited by probenecid.
Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
As a result of administration of cephalexin, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets. Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In haematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the medicine.

Use in Pregnancy

The daily oral administration of cephalexin to rats in doses of 250 or 500 mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, foetal viability, foetal weight, or litter size. Note that the safety of KEFLEX during pregnancy in humans has not been established.
KEFLEX showed no enhanced toxicity in weanling and newborn rats as compared with adult animals. Nevertheless, because the studies in humans cannot rule out the possibility of harm, KEFLEX should be used during pregnancy only if clearly needed.

Nursing Mothers

The excretion of cephalexin in the milk increased up to 4 hours after a 500 mg dose; the medicine reached a maximum level of 4 mg/L, then decreased gradually, and had disappeared 8 hours after administration. Caution should be exercised when cephalexin is administered to a nursing woman.

Adverse Effects

Gastrointestinal

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side effect has been diarrhoea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity

Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson Syndrome, or toxic epidermal necrolysis have been observed.

These reactions usually subsided upon discontinuation of the medicine. In some of the reactions, supportive therapy may be necessary. Anaphylaxis has also been reported. Other reactions have included genital and anal pruritis, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. Reversible interstitial nephritis has been reported rarely. Eosinophilia, neutropenia, thrombocytopenia, haemolytic anaemia and slight elevations in AST and ALT have been reported.

Interactions

KEFLEX may cause a false-positive glucose reaction in urine with Benedict's and Fehlings's solutions and Clinitest® tablets.
Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In haematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the medicine.
As with other ß-lactams, the renal excretion of cephalexin is inhibited by probenecid.
In healthy subjects given single 500 mg doses of cephalexin and metformin, plasma metformin C_{max} and AUC increased by an average of 34% and 24%, respectively, and metformin renal clearance decreased by an average of 14%. No information is available about the interaction of cephalexin and metformin following multiple dose administration.

Overdosage

Signs and Symptoms

Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhoea, and haematuria. If other symptoms are present, it is probably secondary to an underlying disease state, an allergic reaction, or toxicity due to ingestion of a second medication.

Treatment

In managing overdosage, consider the possibility of multiple medicine overdoses, interaction among medicines, and unusual medicine kinetics in your patient.
Unless 5 to 10 times the normal dose of cephalexin has been ingested, gastrointestinal decontamination should not be necessary. Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of medicines from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some medicines that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal. Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of cephalexin; however, it would be extremely unlikely that one of these procedures would be indicated. The oral median lethal dose of cephalexin in rats is 5,000 mg/kg.

Pharmaceutical Precautions

Tablets and Capsules: - Shelf life is three years. Store at room temperature, 15°-30°C. Keep tightly closed.
Suspensions (Granules for): - Shelf life is two years. Store below 30°C.
After reconstitution the suspension should be stored in a refrigerator. It may be kept for 14 days without significant loss of potency. Shake well before using and keep tightly closed.

Medicine Classification

Prescription Medicine.

Package Quantities

Tablets and Capsules: Blister packs each containing 20 tablets.
Suspensions (Granules for): 100mL (when reconstituted).

Further Information

Cephalexin is a 7-(D-α-amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate. Cephalexin has the molecular formula $C_{16}H_{17}N_3O_4S \cdot H_2O$ and the molecular weight is 365.4.
The nucleus of cephalexin is related to that of other cephalosporin antibiotics. The compound is a zwitterion; i.e. the molecule contains both a basic and an acidic group. The isoelectric point of cephalexin in water is approximately 4.5 to 5. The crystalline form of cephalexin which is available is a monohydrate. It is a white crystalline solid having a bitter taste. Solubility in water is low at room temperature; 1 or 2 mg/mL may be dissolved readily, but higher concentrations are obtained with increasing difficulty.
The cephalosporins differ from penicillins in the structure of the bicyclic ring system. Cephalexin has a D-phenylglycyl group as substituent at the 7-amino position and an unsubstituted methyl group at the 3-position.

References

1. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disc Susceptibility Tests--5th ed. Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA, 1993.
2. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically--3rd ed. Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA, 1993.

Name and Address

Eli Lilly and Company (NZ) Limited
9 Gladding Place, Manukau City
P O Box 97 046, South Auckland Mail Centre
Auckland 1730
NEW ZEALAND
Telephone (09) 261 1000

Date of Preparation

1 May 2003

Current Label Artwork

PELLICOLA DI PROPRIETÀ DELLA

Lilly

ELI LILLY ITALIA S.p.A. - Sesto Fiorentino

KEFLEX 125 MG

CODICE PRODOTTO: YL 9414 ITALX

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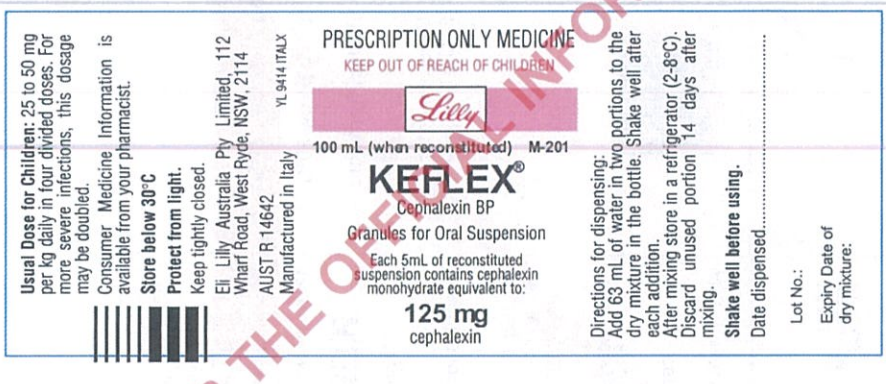
PINKP. 211C	■	LAETUS CODE N° 525	
RED P 185	■		

DIMENSIONS: 120 MM X 47 MM



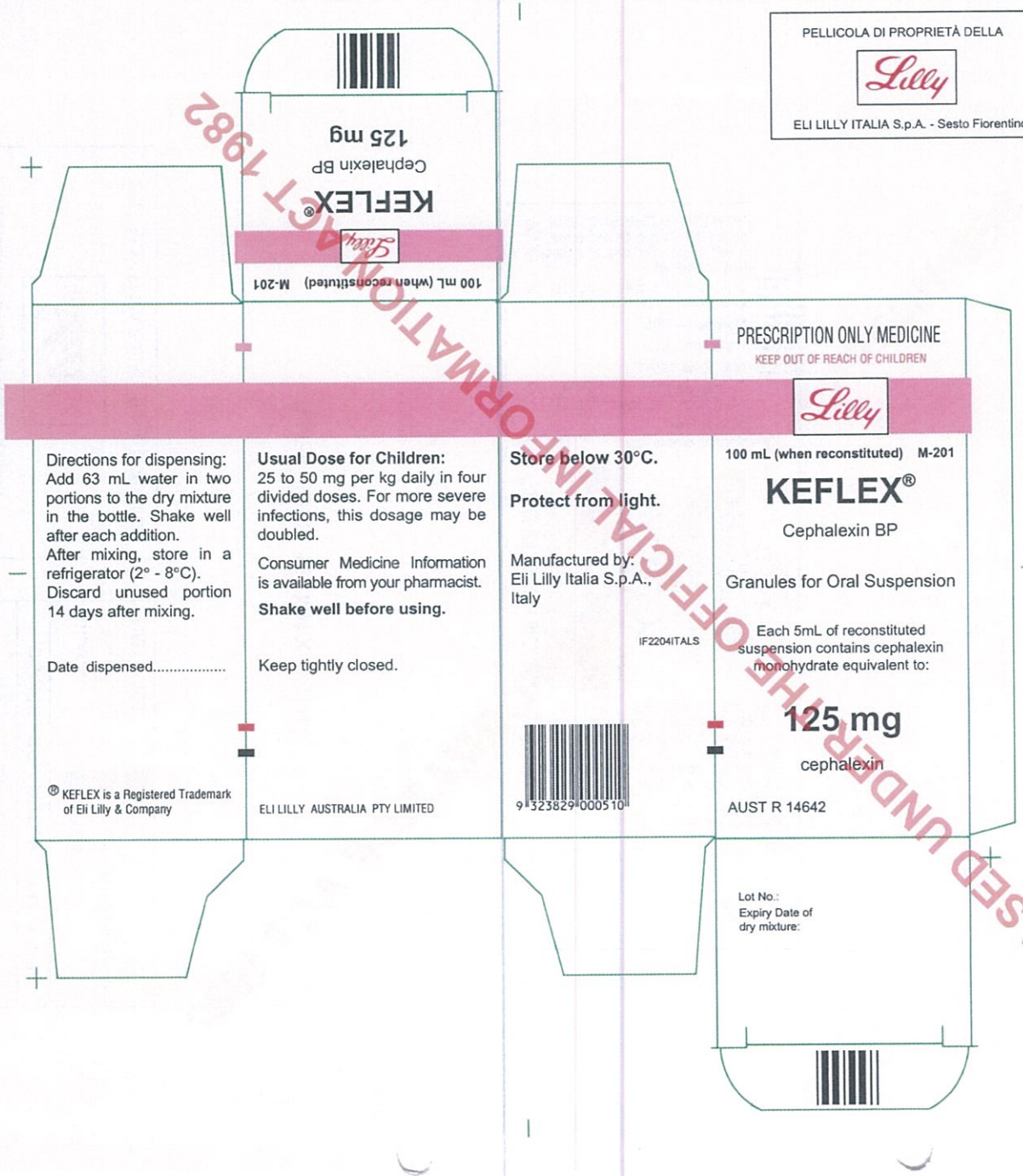
2nd PROOF

MADE BY: CLAUDIA FACCHI DATE: 04 feb 1998

APPROVED BY: _____ DATE: _____

Appendix 2

Current Carton Artwork



PELLICOLA DI PROPRIETÀ DELLA

Lilly

ELI LILLY ITALIA S.p.A. - Sesto Fiorentino

KEFLEX 125 MG	
CODICE PRODOTTO: IF 2204 ITALS	
BLACK	TRACK
PINK 211C	LAETUS CODE N°309
RED 185	
VARNISH	

2nd PROOF

MADE BY: CLAUDIA FACCHI DATE: 04 FEB 1998

Appendix 2

PELLICOLA DI PROPRIETÀ DELLA

Lilly

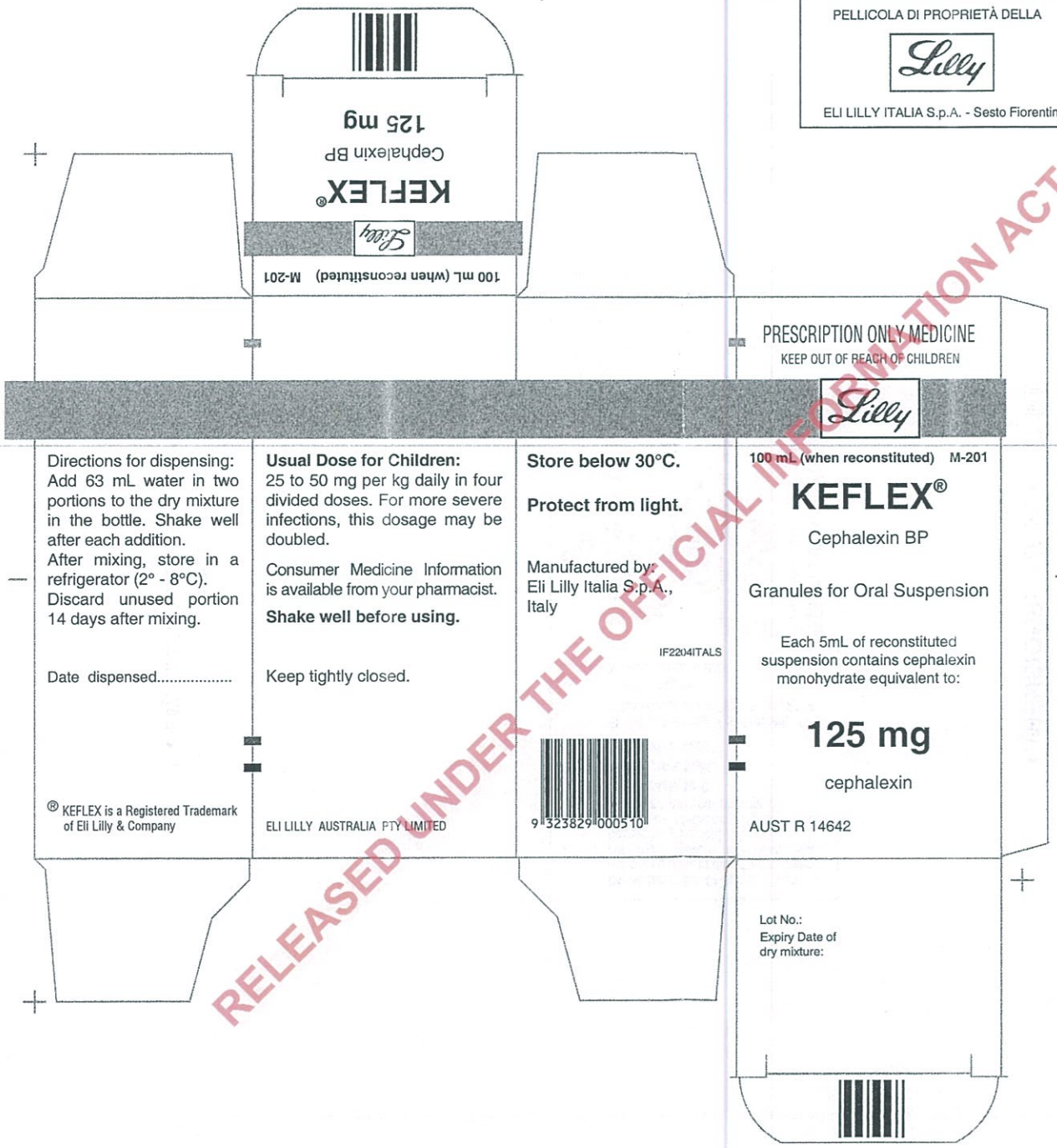
ELI LILLY ITALIA S.p.A. - Sesto Fiorentino

KEFLEX 125 MG

CODICE PRODOTTO: IF 2204 ITALS

BLACK	TRACK
PINK 211C	LAETUS CODE N°309
RED 185	
VARNISH	

Current Carton Artwork
Actual Size



2nd PROOF

MADE BY: CLAUDIA FACCHI DATE: 04 FEB 1998

Current Label Artwork

PELLICOLA DI PROPRIETÀ DELLA

Lilly

ELI LILLY ITALIA S.p.A. - Sesto Fiorentino

KEFLEX 250 MG

CODICE PRODOTTO: YL 8825 ITALX

TRACK
BLACK
RED P 185
LAETUS CODE N°575

DIMENSIONS: 120 MM X 47 MM

1st PROOF

MADE BY: CLAUDIA FACCHI DATE: 28 NOV 1997

Appendix 2

Current Carton Artwork

PELLICOLA DI PROPRIETÀ DELLA

ELI LILLY ITALIA S.p.A. - Sesto Fiorentino

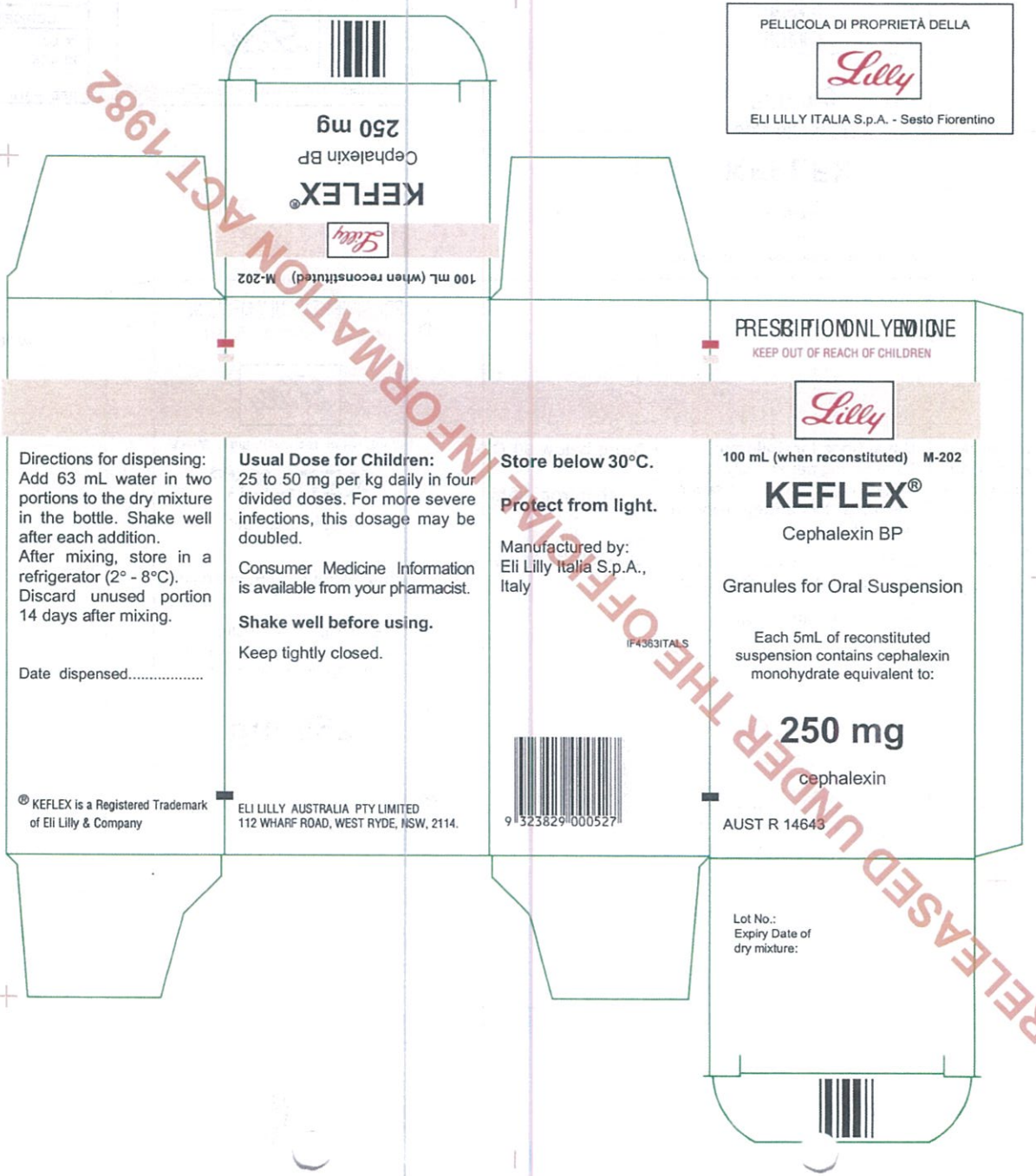
KEFLEX 250 MG

CODICE PRODOTTO: IF 4363 ITALS

TRACK	VARNISH
BLACK	LAETUS CODE N°153
RED P 185	

2nd PROOF

MADE BY: CLAUDIA FACCHI DATE: 01 dec 1997



Current Carton Artwork
Actual Size

PELLICOLA DI PROPRIETÀ DELLA

Lilly

ELI LILLY ITALIA S.p.A. - Sesto Fiorentino

KEFLEX 250 MG

CODICE PRODOTTO: IF 4363 ITALS

TRACK		VARNISH	
BLACK		LAETUS CODE N°153	
ORANGE P1585C			
RED P 185			

2nd PROOF
MADE BY: CLAUDIA FACCHI DATE: 01 dec 1997

Directions for dispensing:
Add 63 mL water in two portions to the dry mixture in the bottle. Shake well after each addition.
After mixing, store in a refrigerator (2° - 8°C).
Discard unused portion 14 days after mixing.

Date dispensed.....

® KEFLEX is a Registered Trademark of Eli Lilly & Company

Usual Dose for Children:
25 to 50 mg per kg daily in four divided doses. For more severe infections, this dosage may be doubled.

Consumer Medicine Information is available from your pharmacist.

Shake well before using.

Keep tightly closed.

ELI LILLY AUSTRALIA PTY LIMITED
112 WHARF ROAD, WEST RYDE, NSW, 2114.

Store below 30°C.

Protect from light.

Manufactured by:
Eli Lilly Italia S.p.A.,
Italy

IF4363ITALS

9 323829 000527

PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Lilly

100 mL (when reconstituted) M-202

KEFLEX®

Cephalexin BP

Granules for Oral Suspension

Each 5mL of reconstituted suspension contains cephalexin monohydrate equivalent to:

250 mg

cephalexin

AUST R 14643

Lot No.:
Expiry Date of dry mixture: