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(54) Title: CEFUROXIME SAFETY KIT

(57) Abstract: The present invention relates to safety kits for intracameral administration of an appropriate dose of cefuroxime subsequent to cataract and other eye surgery. A preferred embodiment of an cefuroxime safety kit according to the invention comprises (a) a perforable sterile vial sterile-filled with a measured amount of cefuroxime, (b) a sterilized reconstitution syringe, and (c) one or more sterilized delivery syringes.

CEFUROXIME SAFETY KIT

FIELD OF THE INVENTION

The invention relates to a kit useful for safe intracameral injection of a precise dose of
5 cefuroxime in patients undergoing ophthalmic surgeries such as cataract surgery.

BACKGROUND OF THE INVENTION

Postoperative endophthalmitis is a feared albeit relatively rare complication of cataract
surgery. The incidences reported in the two large studies discussed below were 0.06 and
10 0.17%, respectively. Infection by bacteria, primarily staphylococci and streptococci, can lead
to legal blindness.

A large study was conducted in Sweden that involved 188,155 patients and addressed the
question of the benefit of intracameral injection of antibiotics during cataract surgery. Wejde
15 et al 2005 Acta Ophthalmol Scand 83: 7-10. The results of the study revealed a reduction of
endophthalmitis by a factor of greater than 4 in patients that had received intracameral
antibiotic. In 98.5% of cases, the antibiotic used was cefuroxime, which antibiotic is active
against gram-positive bacteria. The remaining 1.5% received gentamycin and vancomycin.
Gram-positive bacteria were the dominating aetiology in the endophthalmitis cases
20 observed (84.6% proven by culture).

Results of a large study of the European Society of Cataract & Refractive Surgeons
(ESCRS) were reported in 2007. J Cataract Refract Surg 33: 978-88. The study was carried
out at 24 centers in 9 European countries and included 16,603 patients that underwent
25 phacoemulsification cataract surgery with placement of an intraocular lens. The patients
were assigned to four groups. Group A received no antibiotic prophylaxis. Group B received
intracameral cefuroxime (1 mg in 0.1 ml of normal saline) at the end of surgery. Group C
was administered levofloxacin drops prior and subsequent to surgery. Group D received
both cefuroxime and levofloxacin. Twenty-nine patients experienced endophthalmitis. The
30 study revealed that injection of cefuroxime reduced the risk for endophthalmitis by nearly
five fold. Levofloxacin drops were essentially without effect.

These studies unambiguously demonstrated the considerable benefit of intracameral
injection of cefuroxime. Although cefuroxime has been used widely in ophthalmic practice

for about ten years, there are still no formulations and kits available that were specifically designed or assembled for ophthalmic use. Cefuroxime has limited stability in aqueous solution, in which it hydrolyses at a rate of about 10% in 48 hours (at room temperature). Hence, practitioners currently have to purchase the drug as a bulk powder and have to
5 dissolve and dilute the resulting solution down to the concentration appropriate for prompt intracameral injection. The above-mentioned ESCRS study followed a protocol comprising 16 individual steps for preparing an intracameral injection of cefuroxime. This "kitchen pharmacy" approach is highly inconvenient and time-consuming considering that the cataract procedure itself takes only about 7.5 minutes.

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SUMMARY OF THE INVENTION

The subject invention relates to cefuroxime safety kits for facilitating injection of the antibiotic cefuroxime into the anterior chamber of the eye during or after cataract surgery or other surgical intervention in the anterior part of the eye or into the posterior chamber during or
15 after surgical intervention in the posterior part of the eye.

In one preferred embodiment, the cefuroxime safety kit comprises (1) a perforable sterile vial sterile-filled with a measured amount of cefuroxime and an amount of salt, i.e., sodium chloride, sufficient for producing an isotonic solution upon dissolution, the closure of the vial
20 optionally being protected by a removable cover, (2) a sterilized reconstitution syringe comprising a syringe cylinder that is sterile-prefilled with a sufficient volume of water to dissolve the cefuroxime in the perforable vial to a concentration of 10 mg per ml and a needle protected by a needle shield, whereby the needle is mounted on the reconstitution syringe or is provided separately, and (3) one or more sterilized delivery syringes each
25 comprising a syringe cylinder capable of holding 0.1 ml of ejectable liquid and each complemented with a needle protected by a needle shield, whereby the needle is mounted on the delivery syringe or is provided separately. The perforable sterile vial has either been powder-filled with cefuroxime and salt under sterile conditions or has been filled with a sterile aqueous solution comprising cefuroxime, which solution was subjected to
30 lyophilization. While cefuroxime and salt can be introduced into the vial separately, preferably the two chemicals are introduced as a mixture or in the form of a single solution. Preferably, the perforable vial comprises 5 mg of cefuroxime.

In similar preferred embodiment, the cefuroxime safety kit comprises (1) a perforable sterile vial sterile-filled with a measured amount of cefuroxime, the closure of the vial optionally being protected by a removable cover, (2) a sterilized reconstitution syringe comprising a syringe cylinder that is prefilled with a sufficient volume of isotonic salt solution to dissolve the cefuroxime in the perforable vial to a concentration of 10 mg per ml and a needle protected by a needle shield, whereby the needle is mounted on the reconstitution syringe or is provided separately and (3) one or more sterilized delivery syringes each comprising a syringe cylinder capable of holding 0.1 ml of ejectable liquid and each complemented with a needle protected by a needle shield, whereby the needle is mounted on the delivery syringe or is provided separately. The perforable sterile vial either has been powder-filled with cefuroxime under sterile conditions; was filled with a sterile aqueous solution of cefuroxime, which solution was subjected to lyophilization; or has been filled with a solution of cefuroxime in dimethyl sulfoxide. Preferably, the perforable vial comprises 5 mg of cefuroxime.

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The invention also relates to the use of any of the above cefuroxime safety kits for the preparation of a one mg dose of cefuroxime for intracameral injection, comprising the steps of (a) injecting the entire contents of the reconstitution syringe into the perforable vial comprising cefuroxime, (b) manually shaking said vial to obtain a homogeneous solution of the contents of the closed vial, and (c) withdrawing into the delivery syringe 0.1 ml of solution from said vial. Intracameral injection of the latter volume provides a patient with the desired dose of cefuroxime.

In another embodiment, the cefuroxime safety kit comprises (1) a first perforable sterile vial sterile-filled with a measured amount of cefuroxime and an amount of salt sufficient for producing an isotonic solution upon dissolution, the closure of the vial optionally being protected by a removable cover, (2) a second perforable sterile vial sterile-filled with a volume of water equal to or exceeding that needed for dissolving the cefuroxime in the first perforable vial to a concentration of 10 mg per ml, the closure optionally being protected by a removable cover, (3) a sterilized, empty reconstitution syringe comprising a syringe cylinder capable of holding the volume of ejectable water needed for dissolving the cefuroxime in the first perforable vial to a concentration of 10 mg per ml and a needle protected by a needle shield, whereby the needle is mounted on the reconstitution syringe or is provided separately, and (4) one or more sterilized delivery syringes each comprising a

syringe cylinder capable of holding 0.1 ml of ejectable liquid and each complemented with a needle protected by a needle shield, whereby the needle is mounted on the delivery syringe or is provided separately. The first perforable sterile vial has either been powder-filled with cefuroxime and salt under sterile conditions or has been filled with a sterile aqueous solution comprising cefuroxime, which solution was subjected to lyophilization. Preferably, the first perforable vial comprises 5 mg of cefuroxime.

In another similar embodiment, the cefuroxime safety kit comprises (1) a first perforable sterile vial sterile-filled with a measured amount of cefuroxime, the closure of the vial optionally being protected by a removable cover, (2) a second perforable sterile vial sterile-filled with a volume of sterile isotonic salt solution equal to or exceeding that needed for dissolving or diluting the cefuroxime in the first perforable vial to a concentration of 10 mg per ml, the closure optionally being protected by a removable cover, (3) a sterilized empty reconstitution syringe comprising a syringe cylinder capable of holding the volume of ejectable isotonic salt solution needed for dissolving or diluting the cefuroxime in the first perforable vial to a concentration of 10 mg per ml and a needle protected by a needle shield, whereby the needle is mounted on the reconstitution syringe or is provided separately and (4) one or more sterilized delivery syringes each comprising a syringe cylinder capable of holding 0.1 ml of ejectable liquid and each complemented with a needle protected by a needle shield, whereby the needle is mounted on the delivery syringe or is provided separately. The first perforable sterile vial either has been powder-filled with cefuroxime under sterile conditions; has been filled with a sterile aqueous solution of cefuroxime, which solution was subjected to lyophilization; or has been filled with a solution of cefuroxime in dimethyl sulfoxide. Preferably, the first perforable vial comprises 5 mg of cefuroxime.

The subject invention also relates to the use of a cefuroxime safety kit according to the latter two embodiments for the preparation of a one mg dose of cefuroxime for intracameral injection, comprising the steps of (a) filling the reconstitution syringe with a volume of liquid from the second perforable vial sufficient for dissolving or diluting the cefuroxime in the first perforable vial comprising cefuroxime to a concentration of 10 mg per ml, (b) injecting the entire contents of the filled reconstitution syringe into said first perforable vial, (c) manually shaking said first perforable vial to obtain a homogenous solution of its contents, and (d) withdrawing into the delivery syringe an aliquot of the dissolved contents from said first perforable vial so that the delivery syringe contains 0.1 ml of ejectable solution.

The cefuroxime safety kit according to any of the above embodiments is packaged in a sealed container, whereby individual or grouped components of the kit are sterile-packaged separately. If the cefuroxime safety kit is sterile-packaged in a sealed container, sterile-packaging of individual or grouped components of the kit will no longer be necessary. With any of the afore-mentioned kits, the one or more delivery syringes can be auto-disabled syringes. Similarly, the reconstitution syringe can be an auto-disabled syringe. Each of the afore-mentioned kits will include user instructions.

10 The invention is also considered to encompass alternative and more expensive cefuroxime safety kits such as those described in claims 15-19 as filed.

DETAILED DESCRIPTION OF THE INVENTION

As discussed before, there is a well-established medicinal use of cefuroxime in cataract surgery. Ophthalmic practitioners have been using the antibiotic for a period of at least about ten years. The medical benefits of intracameral administration of the antibiotic during cataract surgery were established by large clinical studies. During all of this time, no dosage form of the antibiotic has been developed for ophthalmic use and made available to practitioners, despite the fact that such a dosage form has been demanded in numerous publications. In addition to the references mentioned in the background section, industrial development of a cefuroxime formulation for the eye (mainly for use in cataract surgery) was urged, e.g., in the following publications: Cimberle in Ocular Surgery News, Europe/Asia-Pacific Edition, January 1, 2008; Daly in Eye World, August 2008; Chang in Cataract and Refractive Surgery Today, May 2006; Cimberle in Ocular Surgery News, U.S. Edition, February 1, 2007; Dalton in Eye World, March 2009; Speaker in Cataract and Refractive Surgery Today, May 2009; survey results published in 2009 in J of Cataract and Refractive Surgery 35: 770-773; Chang et al 2007 J of Cataract and Refractive Surgery 33: 1801-05; Young in Eye World, April 2007, September 2009 & March 2010; Barry in Eye World, May 2007; O'hEineachain in Eurotime, November 2006; Barry in Cataract and Refractive Surgery Today, March 2007 & September 2008; Roach in Eyenet, June 2006; Samaniego in 2009 EyeWorld Asia-Pacific, vol. 5, number 2.

There is an inherent danger of contamination as well as of inadvertent use of an unsafe or inappropriate dose of cefuroxime. These potential dangers have long been recognized and

were memorialized, e.g., in an editorial written by Garcia-Saenz (Arch Soc Esp Ophthalmol 2006; 81: 569-70). A feature story on cataract surgery by Ursell and colleagues asked for "commercial prepackaged doses of cefuroxime" (Cataract and Refractive Surgery Today Europe, Jan/Feb 2007) (see additional references above).

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The safety of intracameral administration of 1 mg of cefuroxime in 0.1 ml of aqueous solution has been established (Montan et al 2002 J Cataract Refract Surg 28: 982-7). However, pharmacokinetic analyses suggest that shortly after administration the mean intracameral concentration of cefuroxime is 2.742 mg/ml (Montan et al 2002). This mean
10 concentration drops to 0.756 mg/ml after one hour and is expected to decrease more slowly thereafter. That the safety margin for 1 mg cefuroxime is relatively narrow, i.e., that significant overdosing can be dangerous, is suggested by a study on human corneal endothelial cells showing that 24-hour exposure to cefuroxime at concentrations exceeding 2.75 mg/ml results in a significant reduction in cell viability (Yoeruek et al 2008 J Cataract
15 Refract Surg 34: 2139-45).

The inventors have developed cefuroxime safety kits for ophthalmic use that are optimized based on the following requirements: (1) The safety kit needs to be a "closed system" so that sterility can be guaranteed. (2) The safety kit needs to allow the user to conveniently
20 and reliably prepare a correct dose of cefuroxime for intracameral injection. (3) Use must be simple and only involve a minimal number of steps so that the possibility of mistakes by the user is reduced to a minimum. Use of the kit should also reduce the systematic error inherent in the preparation of an adequate cefuroxime dose by a hospital pharmacy or a practitioner. (4) Use of the kit should result in a shortening of the time of preparation of a
25 cefuroxime dose compared with current practice; as a consequence, the overall time required for a cataract surgery should be reduced. (5) The kit should be inexpensive in order to encourage practitioners to make use of it, thereby enhancing the safety of cefuroxime preventative therapy. The availability of an inexpensive kit is also expected to convince practitioners that have not used intracameral cefuroxime before to include the antibiotic in
30 their cataract or other ophthalmic procedures with the expected benefit of further reducing the incidence of endophthalmitis.

The preferred kit of the invention comprises, typically in a sealed container, (1) a perforable sterile vial containing a measured amount of sterile-filled cefuroxime or of cefuroxime in

combination with a sufficient amount of salt to generate an isotonic salt solution upon reconstitution, (2) a syringe sterile-prefilled with water (water for injection) in the case salt is already present in the vial, or an isotonic salt solution in the case no salt is present in the vial (reconstitution syringe) and (3) one or more syringes (delivery syringes) for intracameral administration of an appropriate dose of cefuroxime. The kit further comprises shielded needles that are either already mounted on the syringes or provided separately. It will be obvious for the person skilled in the art that most components of the kit are available from different manufacturers. Example prefilled syringes were described in U.S. Pat. Nos. 5,833,653, 7,041,087, 7,331,941 and 7,645,267.

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A typical process for preparing perforable sterile vials containing a measured amount of cefuroxime ($C_{16}H_{16}N_4O_8S$; CAS number 55268-75-2; available from GlaxoSmithKline Ltd.) and salt is as follows: a bulk solution of, e.g., 120 liters, is prepared that contains 10 mg/ml cefuroxime and 0.9% sodium chloride in water purified by distillation or reverse osmosis (water for injection). This solution is passed through one or more sterile filters, the last typically having a pore size of about 0.2 micrometer, and appropriately sized, sterile vials are sterile-filled with 0.5 ml of the filtered cefuroxime solution (batch size of 200'000 vials). The cefuroxime solution in the vials is lyophilized overnight under sterile conditions. Finally, the vials or ampoules (terms used interchangeably) are capped. Different types of perforable ampoules can be utilized. Typically used are crimp top vials that are closed by means of a crimp top seal containing a septum. To avoid surface discoloration of the cefuroxime powder, colored (e.g., amber) or darkly surface-coated vials or ampoules are preferred over clear glass vials or ampoules. It is noted that, if the liquid in the reconstitution syringe is an isotonic salt solution, vials are sterile-filled with a solution of cefuroxime in water. It is further noted that the concentration of cefuroxime in the filling solution does not need to be 10 mg/ml. Depending on sterile-filling equipment available, any concentration of up to 20% w/v in water can be used. The present invention is not limited by any particular method for preparing vials or ampoules containing a measured amount of cefuroxime. Instead of delivery of an aqueous solution containing cefuroxime followed by lyophilization, vials may be powder-filled using microjets that are capable of controlling the amount of powder delivered (e.g., the "Omnidose" microdosing system of Harro Hoefliger, Allmersbach im Tal, Germany). A possible further approach would entail sterile-filling vials with a solution of cefuroxime in dimethyl sulfoxide (up to 10% w/v).

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To prepare a cefuroxime solution for injection into an eye of a patient, the entire volume of liquid contained in the reconstitution syringe is injected into the cefuroxime-containing vial, and the vial is manually agitated to obtain a homogeneous solution of cefuroxime. Preferably, the antibiotic will be present in the vial at a concentration of 10 mg/ml.

5 Preferably, the vial contains 5 mg of cefuroxime and 4.5 mg of sodium chloride or 5 mg of cefuroxime alone, and the reconstitution syringe contains the volume of ejectable water or isotonic salt solution, respectively, needed for preparing a solution containing 10 mg/ml cefuroxime. An aliquot of the cefuroxime solution is then withdrawn from the vial by means

10 of a delivery syringe properly dimensioned for receiving the aliquot. Preferred is a delivery syringe with an ejectable volume of 0.1 ml. The entire volume of cefuroxime solution contained in the delivery syringe is injected intracamerally at the end of a cataract procedure or other ophthalmic surgery. It is noted that the delivery syringe preferably incorporates an auto-disabling mechanism to ensure that the syringe can only be utilized for one injection procedure, thereby reducing the risk of contamination inherent in repeated uses of a

15 syringe. While an auto-disabling feature does not appear to be critical for the reconstitution syringe, embodiments of the kit of the invention may also comprise an auto-disabled reconstitution syringe. The delivery syringe preferably also features a piston stopper.

As discussed before, one embodiment of the preferred kit comprises a perforable, sterile vial

20 containing 5 mg of dry cefuroxime and 4.5 mg of dry sodium chloride, a reconstitution syringe sterile-prefilled with 0.5 ml of ejectable water (water for injection) and a 0.1-ml sterile delivery syringe. Such 0.5-ml reconstitution syringe can be procured, e.g., from Vetter Pharma International USA Inc. (Skokie, IL), "Prefilled Water for Injection (WFI) syringe with tamper-evident closure system V-OVS[®]", supplemented by a shield-protected sterile

25 injection needle, and such delivery syringe, e.g., "auto-disabled syringe 0.1 ml" from Medeco (Abu Dhabi Medical Devices Co., United Arab Emirates). The latter example delivery syringe also incorporates a piston stopping mechanism for preventing overfilling. The delivery syringe and its auto-disabling mechanism are described in the commercial literature, and in U.S. Pat. No. 5,613,951 and European Patent Application No. 064122881. Perforable,

30 sterile vials containing measured amounts of dry cefuroxime can be produced in industrial quantities by contract manufacturers such as Patheon Inc. (Research Triangle Park, NC, or Baar, Switzerland). The components of the kit are presented in an appropriate sealed container typically made from thermoplastic material. Packaging of the kit components into such container may occur under sterile or clean conditions using methods and procedures

well known in the art. User instructions are provided on an outer packaging, added inside the outer packaging, printed on the sealed container containing the kit, or added inside the container. User instructions may be displayed more than once. Other embodiments of the kit may contain up to four 0.1-ml delivery syringes. A single delivery syringe per kit is preferred
5 in the interest of keeping risk of contamination to a minimum. It will be clear to a skilled artisan that equivalent or nearly equivalent kits can be produced by coordinated variation of the dimensions of the kit components. For instance, the amount of cefuroxime in the closed vial could be increased or decreased. If it were, e.g., increased to 10 mg, a 1.0-ml reconstitution syringe would be used to prepare the desired 10 mg/ml cefuroxime solution.
10 Furthermore, the volume of liquid in the reconstitution syringe could be increased or decreased. If a 1.0-ml reconstitution syringe were used to dissolve a 5 mg quantity of cefuroxime, a 0.2-ml delivery syringe would be associated to deliver the target amount of 1.0 mg of cefuroxime to the eye. Such equivalent kits are considered to be within the scope of the present invention. The latter considerations also apply to equivalent or alternative kits
15 described hereinafter.

The safety kit is a "closed" system, which ensures sterility until the time of use. It comprises a perforable, sterile-filled vial containing cefuroxime or cefuroxime and salt, whereby the perforable closure of the vial (e.g., a septum or a stopper) is preferably protected from
20 contamination by a removable cover. It further includes a reconstitution syringe containing sterile-filled diluent, i.e., water or an isotonic salt solution. The ejection port of the syringe is protected by a cover. A sterile-packaged syringe needle protected by a shield is provided separately. Alternatively, a sterile needle is mounted directly on the reconstitution syringe, its sterility ensured by a needle shield. Furthermore, the kit includes a sterile delivery syringe
25 with attached needle that is also protected by a needle shield. Alternatively, delivery syringe and shielded needle are provided separately. The components of the kit are assembled and packaged in a sealed container. Although this is not required, the latter assembly and packaging preferably is performed under sterile conditions. Such sterile assembly makes sterile-packaging of the various components optional. If assembly and packaging in the
30 sealed container is not performed under sterile conditions, kit components are individually sterile-packaged, e.g., in blister packs.

The safety kit allows the user to conveniently and reliably prepare an appropriate dose of cefuroxime for intracameral injection. An appropriate dose is 1 mg cefuroxime as used in the

large clinical studies referenced above. Besides the removal of protective packaging, covers and needle shields and, in some embodiments, attachment of needles to syringes, preparation of an appropriate dose of cefuroxime using the kit involves three simple steps. The first step is injection of the entire contents of the reconstitution syringe through the septum or stopper of the cefuroxime-containing vial. Step two involves manual shaking of the vial for a prescribed number of times resulting in a homogeneous solution of cefuroxime. The final step is filling of the delivery syringe with cefuroxime solution from the cefuroxime-containing vial. The correct dose of cefuroxime (1 mg) is delivered by intracameral injection of the entire contents of the delivery syringe.

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Use of the safety kit greatly reduces the possibility of significant user error. The volume of liquid contained in the reconstitution syringe is that required for preparing a 10mg/ml cefuroxime solution in the drug-containing vial. Hence, the user only needs to empty the reconstitution syringe into the cefuroxime-containing vial. Errors in reading graduations that could occur, if only a fraction of the liquid was to be injected, are avoided. The delivery syringe is so marked that significant accidental overfilling due to misreading of a graduation should not occur. Preferably, a piston stopping mechanism is present in the delivery syringe to prevent accidental overfilling altogether. The entire contents of the delivery syringe will have to be delivered to the eye in order to deposit the correct dose. No graduations on the syringe need to be read and interpreted during drug delivery to the eye.

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The kit significantly reduces the errors inherent in the preparation of an appropriate cefuroxime dose by a hospital pharmacy or a practitioner. As mentioned previously, the protocol used in the ESCRS study for preparing an appropriate cefuroxime dose encompassed 16 different steps. There is a possibility for accidental errors (mistakes of preparer) and systemic errors (small errors due to unavoidable inaccuracies) at 8 of these steps. Assuming that the amount of cefuroxime in the drug-containing vial and the volume of liquid in the prefilled reconstitution syringe are correct (as a result of quality control by the manufacturer), there are only 2 steps at which accidental errors can be made when using the kit for preparing a cefuroxime dose. A systemic error can only occur at one step. Hence, use of the kit will dramatically reduce accidental and systemic errors that affect the cefuroxime dose delivered to the eye and will, therefore, increase the safety of the prophylactic regimen.

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Handling of the kit is simple compared to the preparation of an appropriate cefuroxime dose by a practitioner or his laboratory or pharmacy. As discussed above, the 16 steps prescribed by the ESCRS study are replaced in the kit by the removal of protective covers from drug vial, syringes and needles (and possible attachment of needle(s) to syringe(s)), and three
5 easy manipulations. This dramatic decrease in complexity of manipulations will reduce the workload of the practitioner and/or eliminate the need for coordinated pharmacy activity. The availability of a safety kit for cefuroxime in the marketplace will also lead practitioners who have not used cefuroxime before, be it because of the inconvenience of custom preparation of appropriate doses or because of concerns about possible mistakes that may happen
10 during such custom preparation of cefuroxime doses, to make use of this prophylactic regimen that has been proven to reduce the occurrence of endophthalmitis.

The cefuroxime safety kit should be inexpensive to produce. The lower the price of a kit, the greater will be the likelihood that practitioners will make use of it instead of foregoing
15 cefuroxime prophylaxis or preparing cefuroxime doses themselves with the attendant risk of errors and the possible dangers of contamination and overdosing (danger of cytotoxic effects) or underdosing (lack of efficacy; danger of enhancing the development of bacterial resistance) the patient. The above-described preferred kit represents a very low-cost as well as an efficient solution, because its components are comparatively simple to manufacture as
20 well as are readily available from suppliers.

Another embodiment of a cefuroxime safety kit of the invention is identical to the preferred kit described above, except that the prefilled reconstitution syringe is replaced by an unfilled reconstitution syringe, preferably a 0.5-ml auto-disabling reconstitution syringe (e.g., from
25 Medeco), and a second perforable, sterile vial sterile-filled with water or isotonic salt solution (> 0.5 ml). The operation of this kit is very similar to that of the preferred kit except for the additional step of filling the reconstitution syringe from the vial containing water or salt solution. This kit is less preferred because of the latter additional required step and the attendant additional systematic error and the possibility of additional user error and risk of
30 contamination.

Other solutions to the problem of assembling an optimal cefuroxime safety kit are provided as well. However, primarily because they incorporate more complex and, therefore, generally more expensive technology, these kits may not be as cost-effective as the

preceding kits. For example, use can be made of a two-chamber or mixing syringe. Such syringes are capable of holding dry cefuroxime or cefuroxime and salt in one compartment and diluent, i.e., water or an isotonic salt solution, in the other chamber, and of mixing the contents of the two chambers to produce a desired cefuroxime solution. Example two-chamber syringes were described in U.S. Pat. Nos. 3,327,710; 3,380,451; 4,581,016; 4,874,381; 5,779,668; 6,419,656; 6,770,052 and 6,817,987; U.S. reexamined Pat. No. 35986, and European Patent Application No. 112574. Two-chamber syringes can be obtained from several sources, including from Vetter Pharma (Lyo-Ject^R). In particular, a safety kit for administering the desired dose of cefuroxime (1 mg) to an eye of a patient can comprise a two-chamber syringe sterile-filled with 1 mg of cefuroxime or cefuroxime and salt sufficient to produce an isotonic solution upon dissolution, and containing in the second chamber an ejectable volume of 0.1 ml of sterile water or isotonic salt solution (if the first chamber does not include salt). Mounted on the syringe would be an injection needle protected by a shield. Alternatively, a sterile shielded needle could be provided separately. The kit can be packaged, in a clean or sterile fashion, in a container as described before for the preferred safety kit. User instructions would also be provided with the kit.

A similar safety could comprise a two-chamber syringe, a perforable, empty sterile vial or ampoule capable of holding at least 0.5 ml of liquid and one or more 0.1-ml delivery syringes. Shielded sterile needles could be mounted on the syringes or provided separately. The two-chamber syringe would contain 5 mg of dry cefuroxime or 5 mg of cefuroxime and salt sufficient to produce an isotonic solution upon dissolution in one chamber and 0.5 ml of ejectable sterile water or isotonic salt solution as the case may be in the other chamber. Upon activation of the syringe mechanism, the contents of the two chambers would be mixed, and the resulting isotonic cefuroxime solution could be ejected into the empty sterile vial. One or more delivery syringes would be filled with 0.1 ml cefuroxime solution from the latter vial. The kit would be packaged, in a clean or sterile fashion, in a container as described before for the preferred safety kit. User instructions would also be provided with the kit.

A further alternative cefuroxime safety kit can comprise a single-chamber syringe prefilled with 0.1 ml of ejectable water (or isotonic salt solution), upon which syringe could be mounted a flow control device such as described in U.S. Pat. Nos 6,379,340 and 6,238,372 and distally to the device a sterile, shielded needle. Flow control devices of the type

disclosed in the latter patents are commercialized under the trade name MixJect by West Pharmaceutical Service Inc. (Lionville, PA). The flow control devices have three ports, one for a prefilled syringe, the other for an injection needle and the third adapted to fit over the top of a vial and capable of penetrating the septum or stopper of the vial. In addition to this
5 prefilled syringe-flow control device-needle assembly, the safety kit would comprise a perforable sterile vial sterile-filled with 1 mg of cefuroxime and a sufficient amount of salt for reconstitution of an isotonic cefuroxime solution (or with 1 mg of cefuroxime alone if the syringe is prefilled with an isotonic salt solution). A user of this kit would first mount the prefilled syringe-flow control device-needle assembly on the cefuroxime-containing vial. By
10 advancing the plunger of the syringe, the user would inject the entire contents of the syringe into the latter vial. The cefuroxime solution would be reconstituted by gentle agitation of the entire assembly. With the vial in an inverted position, the plunger could be retracted to fill the syringe body with the reconstituted cefuroxime solution. Subsequent to removal of the vial and part of the flow control device, the user could retain the needle-fitted syringe filled with
15 the cefuroxime solution. Forward movement of the plunger would cause the cefuroxime solution to be ejected through the needle.

In another embodiment, the cefuroxime-containing vial and the prefilled reconstitution syringe with associated needle of the preferred safety kit would be replaced a device that
20 incorporates a perforable vial sterile-filled with cefuroxime powder (e.g., 5 mg), a container holding an appropriate volume of isotonic salt solution (e.g., 0.5 ml) and a mechanism that upon actuation releases the salt solution into the dry cefuroxime-containing vial for reconstitution. Subsequent to removal of the perforable vial from the device, a delivery syringe(s) would be used to withdraw 0.1 ml of cefuroxime solution, representing a single
25 dose for intracameral injection. Suitable devices of the aforementioned type are commercially available, e.g., Act-0-Vial from Pfizer CentreSource (Kalamazoo, MI). Other related devices include two-chamber perforable vials, wherein the chambers are separated by an insulating spacer that can be dislodged or displaced by an actuating mechanism to allow mixing of solid and liquid contents of the two chambers. The reconstituted solution can
30 then be withdrawn by means of a delivery syringe. A device of this type is manufactured by Degill International Corp. of Taiwan under the name of "EZ Fusion two-in-one". An alternative cefuroxime safety kit could include the latter device sterile-prefilled in one chamber with 5 mg of cefuroxime and a sufficient quantity of salt to reconstitute an isotonic solution and 0.5 ml of water-for-injection in the other chamber. Additionally, the kit would

include one or more 0.1-ml sterile delivery syringes with mounted or associated sterile, shielded needles. The kit would be assembled and packaged in a container and contain user information as described before for the preferred safety kit.

CLAIMS

1. Cefuroxime safety kit, comprising
 - 5 (a) A perforable sterile vial sterile-filled with a measured amount of cefuroxime and an amount of salt sufficient for producing an isotonic solution upon dissolution, the closure of the vial optionally being protected by a removable cover,
 - 10 (b) A sterilized reconstitution syringe comprising a syringe cylinder that is sterile- prefilled with a sufficient volume of water to dissolve the cefuroxime in the perforable vial to a concentration of 10 mg per ml and a needle protected by a needle shield, and
 - (c) One or more sterilized delivery syringes each comprising a syringe cylinder capable of holding 0.1 ml of ejectable liquid and each complemented with a needle protected by a needle shield.
- 15 2. The cefuroxime safety kit of claim 1, wherein the perforable sterile vial was powder-filled with cefuroxime and salt under sterile conditions or was filled with a sterile aqueous solution comprising cefuroxime, which solution was subjected to lyophilization.
3. Cefuroxime safety kit, comprising
 - 20 (a) A perforable sterile vial sterile-filled with a measured amount of cefuroxime, the closure of the vial optionally being protected by a removable cover,
 - (b) A sterilized reconstitution syringe comprising a syringe cylinder that is prefilled with a sufficient volume of isotonic salt solution to dissolve the cefuroxime in the perforable vial to a concentration of 10 mg per ml and a
25 needle protected by a needle shield, and
 - (c) One or more sterilized delivery syringes each comprising a syringe cylinder capable of holding 0.1 ml of ejectable liquid and each complemented with a needle protected by a needle shield.
4. The cefuroxime safety kit of claim 3, wherein the perforable sterile vial either was
30 powder-filled with cefuroxime under sterile conditions; was filled with a sterile aqueous solution of cefuroxime, which solution was subjected to lyophilization; or was filled with a solution of cefuroxime in dimethyl sulfoxide.
5. The cefuroxime safety kits of claims 1-4, wherein the perforable vial comprises 5 mg of cefuroxime.

6. Use of a cefuroxime safety kit according to claims 1-5 for the preparation of a one mg dose of cefuroxime for intracameral injection, comprising the steps of
- (a) Injecting the entire contents of the reconstitution syringe into the perforable vial comprising cefuroxime,
 - 5 (b) Manually shaking said vial to obtain a homogeneous solution of the contents of the closed vial, and
 - (c) Withdrawing into the delivery syringe 0.1 ml of solution from said vial.
7. A cefuroxime safety kit according to claim 1 or 2, wherein the prefilled reconstitution syringe is replaced by
- 10 (a) A second perforable sterile vial sterile-filled with a volume of water equal to or exceeding that needed for dissolving the cefuroxime in the first perforable vial to a concentration of 10 mg per ml, the closure optionally being protected by a removable cover, and
 - (b) A sterilized, empty reconstitution syringe comprising a syringe cylinder
 - 15 capable of holding the volume of ejectable water needed for dissolving the cefuroxime in the first perforable vial to a concentration of 10 mg per ml and a needle protected by a needle shield.
8. A cefuroxime safety kit according to claim 3 or 4, wherein the prefilled reconstitution syringe is replaced by
- 20 (a) A second perforable sterile vial sterile-filled with a volume of sterile isotonic salt solution equal to or exceeding that needed for dissolving or diluting the cefuroxime in the first perforable vial to a concentration of 10 mg per ml, the closure optionally being protected by a removable cover, and
 - (b) A sterilized empty reconstitution syringe comprising a syringe cylinder
 - 25 capable of holding the volume of ejectable isotonic salt solution needed for dissolving or diluting the cefuroxime in the first perforable vial to a concentration of 10 mg per ml and a needle protected by a needle shield.
9. The cefuroxime safety kit of claim 7 or 8, wherein the first perforable vial comprises 5 mg of cefuroxime.
- 30 10. Use of a cefuroxime safety kit according to claims 7-9 for the preparation of a one mg dose of cefuroxime for intracameral injection, comprising the steps of
- (a) Filling the reconstitution syringe with a volume of liquid from the second perforable vial sufficient for dissolving or diluting the cefuroxime in the first perforable vial to a concentration of 10 mg per ml,

- (b) Injecting the entire contents of the filled reconstitution syringe into said first performable vial,
- (d) Manually shaking said first performable vial to obtain a homogenous solution of its contents, and
- 5 (e) Withdrawing into the delivery syringe an aliquot of the dissolved contents from said first performable vial so that the delivery syringe contains 0.1 ml of ejectable solution.
11. The cefuroxime safety kit of any of claims 1-5 and 7-9 packaged in a sealed container, whereby individual or grouped components of the kit are sterile-packaged
- 10 separately.
12. The cefuroxime safety kit of any of claims 1-5 and 7-9 sterile-packaged in a sealed container.
13. The cefuroxime safety kit of any of claims 1-5 and 7-9, wherein the one or more delivery syringes are auto-disabled syringes.
- 15 14. The cefuroxime safety kit of any of claims 1-5 and 7-9, wherein the reconstitution syringe is an auto-disabled syringe.
15. A sterilized two-chamber syringe comprising in one chamber 1 mg of cefuroxime powder and in the other chamber 0.1 ml of water or aqueous solution, the syringe comprising a mechanism for enabling communication between the two chambers to
- 20 allow reconstitution of a sterile cefuroxime solution and for ejecting the solution through a needle port, the syringe being complemented with a shielded sterile needle.
16. Cefuroxime safety kit, comprising
- (a) A sterilized two-chamber syringe comprising in one chamber a measured amount
- 25 of cefuroxime powder and in the other chamber a sufficient volume of water or aqueous solution to prepare a 10mg/ml solution of cefuroxime, the syringe comprising a mechanism for enabling communication between the two chambers to allow reconstitution of a sterile cefuroxime solution and for ejecting the solution through a needle port, the syringe being complemented with a shielded sterile
- 30 needle,
- (b) A performable sterile empty vial capable of holding the reconstituted cefuroxime solution from the sterilized two-chamber syringe, the closure optionally being protected by a removable cover, and

- (c) One or more sterilized delivery syringes each comprising a syringe cylinder capable of holding 0.1 ml of ejectable liquid and each complemented with a needle protected by a needle shield.

17. Cefuroxime safety kit, comprising

- 5 (a) A sterilized syringe prefilled with 0.1 ml of ejectable water or aqueous solution, which syringe is connected to a first port of a flow control device,
- (b) A perforable sterile vial comprising 1 mg of cefuroxime, the vial being connected to a second port of the flow control device the second port incorporating a needle that pierces the perforable cover of the vial, and
- 10 (c) A sterile needle protected by a needle shield, the needle being connected to a third port of the flow control device,
- whereby actuation of the plunger of the syringe causes the water or aqueous solution contained in the syringe to be transferred to the vial via first and second ports to reconstitute a cefuroxime solution, subsequent retraction of the plunger results in the transfer of the cefuroxime solution to the syringe and further
- 15 actuation of the plunger subsequent to detachment of the vial and closure of the second port results in the ejection of the cefuroxime solution through the third port.

18. Cefuroxime safety kit, comprising

- 20 (a) A perforable sterile vial comprising a measured amount of cefuroxime,
- (b) A container sterile-prefilled with a sufficient volume of water or aqueous solution to dissolve the cefuroxime in the perforable vial to a concentration of 10 mg per ml, the container being removably connected with the perforable vial and comprising a mechanism allowing for the deliberate release of the
- 25 entire volume of water or aqueous solution into the perforable vial, and
- (c) One or more sterilized delivery syringes each comprising a syringe cylinder capable of holding 0.1 ml of ejectable liquid and each complemented with a needle protected by a needle shield.

19. Cefuroxime kit, comprising

- 30 (a) A sterile cartridge perforably closed at one end, the cartridge comprising two separated chambers of which one contains a measured amount of cefuroxime powder and the other a sufficient volume of water or aqueous solution to dissolve the cefuroxime to a concentration of 10 mg per ml, the chambers separated by a divider and the cartridge incorporating a

mechanism for displacing the divider to allow communication between the chambers and reconstitution of a cefuroxime solution, and

- (b) One or more sterilized delivery syringes each comprising a syringe cylinder capable of holding 0.1 ml of ejectable liquid and each complemented with a needle protected by a needle shield.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/000848

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61M5/178 A61M5/315 A61J1/20
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K A61M A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Cefuroxim: 10 100 - 10 106" In: Bundesverband der Pharmazeutischen Industrie: "Rote Liste 2003", 1 January 2003 (2003-01-01), Rote Liste Service GmbH, Frankfurt / Main, XP002663948, ISBN: 3-87193-268-X abstract -----	1-19
X	"Caverject 10micro g/-20 micro g: 82 216" In: Bundesverband der Pharmazeutischen Industrie: "Rote Liste 2003", 1 January 2003 (2003-01-01), Rote Liste Service GmbH, Frankfurt/Main, XP002663949, ISBN: 3-87193-268-X abstract ----- -/--	1-19

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 21 November 2011	Date of mailing of the international search report 09/12/2011
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Giese, Hans-Hermann
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/000848

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 478 771 B1 (LAVI GILAD [IL] ET AL) 12 November 2002 (2002-11-12) paragraphs [0007], [0008] -----	1-19
A	US 3 380 451 A (PORTER ROBERT E ET AL) 30 April 1968 (1968-04-30) claim 1 -----	1-19
A	WO 96/30066 A1 (ABBOTT LAB [US]) 3 October 1996 (1996-10-03) claim 1 -----	1-19
A	US 3 327 710 A (DE SANTO JOHN ET AL) 27 June 1967 (1967-06-27) the whole document -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/000848

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6478771	B1	12-11-2002	US 6478771 B1 12-11-2002
			US 2002004643 A1 10-01-2002
			US 2003023203 A1 30-01-2003

US 3380451	A	30-04-1968	NONE

WO 9630066	A1	03-10-1996	AT 252400 T 15-11-2003
			AU 712959 B2 18-11-1999
			AU 5373796 A 16-10-1996
			CA 2216926 A1 03-10-1996
			DE 69630444 D1 27-11-2003
			DE 69630444 T2 12-08-2004
			DK 821599 T3 01-03-2004
			EP 0821599 A1 04-02-1998
			ES 2210355 T3 01-07-2004
			JP 3803934 B2 02-08-2006
			JP H11504536 A 27-04-1999
			PT 821599 E 31-03-2004
			WO 9630066 A1 03-10-1996

US 3327710	A	27-06-1967	NONE
