

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No 1901/2006, as
amended**

Dexamethasone combinations

MT/W/0006/pdWS/001

Rapporteur:	Malta
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Dexamethasone combination products (eye/ear drops, eye ointments) <i>Refer to Line listing (13th wave List with studies)</i>
INN (or common name) of the active substance(s):	Dexamethasone combinations: <u>I. Sanofi-aventis:</u> - Dexamethasone + Framycetin + Gramicidin <u>II. Alcon:</u> - Dexamethasone + Tobramycin - Dexamethasone + Chloramphenicol - Dexamethasone + Gentamycin + Tetrazyline hydrochloride - Dexamethasone + Diphenhydramine hydrochloride - Dexamethasone + Neomycin sulphate - Dexamethasone + Neomycin + Polymyxin B sulphate - Dexamethasone + Tramazoline hydrochloride
MAH (s):	- Alcon and its subsidiaries - Sanofi – aventis <i>(Refer to Section V. of this PAR)</i>
Pharmaco-therapeutic group (ATC Code):	D07CB04 S01AA20 S01BB05 S01CA01 S01CA06 S02CA06 S03CA01
Pharmaceutical form(s) and strength(s):	Eye drops Eye ointment Ear drops

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I. EXECUTIVE SUMMARY

Dexamethasone is a potent corticosteroid which suppresses the inflammatory response to a variety of agents which delay or slow healing. The strong anti-inflammatory and immunosuppressive effects of glucocorticoids are mediated primarily by the cytosolic glucocorticoid receptors, which act to increase the expression of anti-inflammatory proteins and decrease the production of pro-inflammatory proteins. Glucocorticoids also exert a number of non-genomic, rapid actions independent of gene transcription regulation, including the inhibition of the release of inflammatory PGE₂ and the blocking of T cell receptor signalling.

Dexamethasone can be used alone for short term local treatment of inflammation and in combination with a number of topical antibiotics to control Acute Otitis Externa (AOE) and eye diseases for short term application in the treatment of steroid responsive conditions of the eye, when prophylactic antibiotic treatment is also required, after excluding the presence of fungal and viral disease.

In October 2011, two MAHs (Sanofi-aventis, Alcon) submitted a list of literature references of paediatric clinical data discussing and investigating the use of dexamethasone eye/ear combinations in the paediatric patients as part of this European paediatric work-sharing procedure under Article 45 of Regulation EC 1901/2006 as amended.

Most of the eye/ear preparations presented in this Article 45 procedure are not indicated for paediatric use. The antibiotics concerned are indicated for use in children on their own however, three preparations are licensed for use in paediatrics.

Changes are proposed to section 4.2 and 4.4 of the SmPC for the Dexamethasone + framycetin + gramicidin combinations.

Summary of outcome

- ☐ No change
- ☒ Change: **for Dexamethasone + framycetin + gramicidin**
- ☐ New study data
- ☐ New safety information
- ☒ Paediatric information clarified: **section(s) 4.2 and 4.4 for Dexamethasone + framycetin + gramicidin combinations.**
- ☐ New indication

II. RECOMMENDATION

SmPC and Patient information leaflets (PL) changes were initially proposed by the Rapporteur in sections 4.2 and 4.4 for the Dexamethasone + framycetin + gramicidin combination and in section 4.1 and 4.2 for the Dexamethasone + neomycin + polymyxin B sulphate combinations.

FINAL RECOMMENDATION (refer to page 28): Only the final recommendations for section 4.2 and 4.4 for the Dexamethasone + framycetin + gramicidin combinations (with respective changes to section 3 of the PIL) are to be taken into consideration for this work sharing procedure.

III. INTRODUCTION

On 11 October 2011, Sanofi-aventis and Alcon submitted the following documents for Dexamethasone combinations in accordance with Article 45 of the Regulation (EC) No. 1901/2006, as amended on eye/ear preparations for paediatric use:

- Covering letter
- A short clinical expert overview of the submitted clinical data from both MAH's concerned.
- A list of literature references regarding the use of dexamethasone in the paediatric population for each combination.

The following Dexamethasone combinations for eye/ear preparations have been presented:

- Dexamethasone + Framycetin + Gramicidin (Sanofi)
- Dexamethasone + Tobramycin (Alcon)
- Dexamethasone + Chloramphenicol (Alcon)
- Dexamethasone + Gentamycin + Tetrazyline hydrochloride (Alcon)
- Dexamethasone + Diphenhydramine hydrochloride (Alcon)
- Dexamethasone + Neomycin sulphate (Alcon)
- Dexamethasone + Neomycin + Polymyxin B sulphate (Alcon)
- Dexamethasone + Tramazoline hydrochloride (Alcon)

In addition, the following documentation has been included as per the procedural guidance:

- A line listing (*13th wave List with studies*)
- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product in all member states, and related PL wording

No non-clinical /clinical data has been submitted for the dexamethasone / diphenhydramine hydrochloride combination.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Dexamethasone is available in a number of combinations for eye and ear preparations in the form of ointments and/or drops. The following combinations are subject to this paediatric work sharing procedure:

➤ **Dexamethasone + Framycetin + Gramicidin (Sanofi)**

The MA was granted in Denmark in 1962 and the fixed combination is now marketed in about 40 countries including the following EU countries: Denmark, Malta, Iceland, Ireland, The Netherlands, Norway and the UK.

The fixed combination is indicated for:

In the eye: Short term treatment of steroid responsive conditions of the eye when prophylactic treatment is also required, after excluding the presence of fungal and viral disease.

In the ear: Otitis Externa

Application to the eyelid: Blepharitis

The fixed dose combination is available as ear/eye drops solution (0.5% w/v of framycetin sulphate, 0.05% w/v of dexamethasone and 0.005% w/v of gramicidin) and ear/eye ointment (0.5% w/w of framycetin sulphate, 0.05% w/w of dexamethasone and 0.005% w/w of gramicidin) for auricular and ocular use.

The excipients in Sofradex ear/eye drops include citric acid, sodium citrate, lithium chloride, phenylethyl alcohol, industrial methylated spirit, polysorbate 80 and purified water.

Paediatric information:

The Sofradex dosage form, eye/ear drops, is suitable for use in the paediatric population. The formulation does contain a preservative: phenylethanol at 0.6% w/v. However, there is no regulatory guidance that prohibits paediatric exposure to this preservative. The paediatric indication is eczematous inflammation in otitis externa and local treatment of inflammation.

➤ **Dexamethasone + Tobramycin (Alcon, Tobradex suspension and ointment)**

The combination is indicated in steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial infection exists or a risk of bacterial ocular infection exists.

The combination is available as eye drops suspension and eye ointment (1 ml of suspension contains 3 mg tobramycin and 1 mg dexamethasone).

Paediatric information:

Tobramycin is indicated in children but is not recommended for use in combination with dexamethasone.

The SmPC for Tobradex states:

TOBRADEX is not recommended for use in children and adolescents less than 18 years of age.

Rapporteur comment: On the 2nd of August 2012 a PAR relating to a parallel worksharing procedure concerning tobramycin combination products was published. A change in indication and product information was proposed as shown below and agreed by the member states. As a result of this a Type IB variation to amend Tobradex suspension and ointment will be submitted. This will be dealt with by the tobramycin worksharing procedure FI/W/002/pdWS/001 and is only updated here for information.

Tobradex suspension and ointment**4.1 Therapeutic indications**

Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults and children aged 2 years and older.

4.2 Posology and method of administration**Paediatric population**

Tobradex suspension and ointment may be used in children 2 years of age and older at the same dose as in adults. Currently available data is described in Section 5.1. The safety and efficacy in children younger than 2 years of age have not been established, and no data are available.

4.4 Special warnings and precautions for use

It is advisable that the intraocular pressure be checked frequently. This is especially important in paediatric patients receiving dexamethasone-containing products, as the risk of steroid-induced ocular hypertension may be greater in children below 6 years of age and may occur earlier than a steroid response in adults. The frequency and duration of treatment should be carefully considered, and the IOP should be monitored from the outset of treatment, recognizing the risk for earlier and greater steroid-induced IOP increases in the paediatric patients.

5.1 Pharmacodynamic properties**Paediatric Population**

The safety and efficacy of Tobradex eye drops and eye ointment in children have been established by broad clinical experience, but only limited data are available. In a clinical study of Tobradex suspension for the treatment of bacterial conjunctivitis, 29 paediatric patients, ranging in age from 1 to 17 years, were treated with 1 or 2 drops of Tobradex every 4 or 6 hours for 5 or 7 days. In this study, differences in the safety profile between adult and paediatric patients were not observed.

➤ **Dexamethasone + Chloramphenicol (Alcon)**

The product was first authorised in Spain in January 1965 and is indicated for the following conditions:

1. Inflammatory conditions of the anterior pole of the eye, produced by, or associated with infections caused by microorganisms susceptible to chloramphenicol.
2. Allergic inflammations associated to infection.
3. Acute and chronic conjunctivitis, non-ulcerous keratitis and ocular postoperative treatment.

The fixed combination is available as an eye ointment or eye drops as shown below:

Chloramphenicol sodium succinate 7.3 mg/ml and dexamethasone sodium phosphate 1 mg/ml; eye drops solution.

Chloramphenicol 10 mg/g and dexamethasone 0.5 mg/g eye ointment

Chloramphenicol is a synthetic broad-spectrum antibiotic originally isolated from certain strains of *Streptomyces venezuelae*. It is primarily bacteriostatic and acts by inhibition of protein synthesis.

Paediatric information:

Although chloramphenicol is used in children, the dexamethasone combination product is not indicated for use in children.

➤ **Dexamethasone + Gentamycin + Tetrylozine hydrochloride (Alcon)**

The fixed combination was first authorised in Spain in May 1973 and is available as ear and eye drops as shown below:

Gentamicin sulphate 3 mg/ml, dexamethasone sodium phosphate 1 mg/ml and tetryzoline hydrochloride 1mg/ml; ear/eye drops, solution.

The indications are as follows:

Eye: Topical treatment of anterior chamber infections of the eye with inflammatory component caused by microorganisms sensitive to gentamycin. Infectious and allergic blepharoconjunctivitis and conjunctivitis.

Ear: Ear infections such as external otitis and in all conditions in which a corticosteroid antibiotic therapy is indicated.

Paediatric information:

The use of this combination in children is not included in the contraindications of the current SmPC however there is no available specific clinical data to support the use of the indications in children. This is stated in the SmPC.

➤ **Dexamethasone + Neomycin sulphate (Alcon)**

The combination was first authorised in Greece in January 1968 is available as an ointment in the following strengths:

Dexamethasone sodium sulphate 0.55 mg/g and neomycin sulphate 7.88 mg/g combination eye ointment (and dexamethasone 1 mg/g and neomycin sulphate 7.88 mg/g combination ointment for skin disorders).

The product is indicated for the following conditions:

Eye: Blepharitis, conjunctivitis and keratitis. Treatment after penetration of foreign bodies and after their removal. Allergic and non infectious irritation of the eye with the possibility of infection.

Ointment: Skin disorders that require weak topical corticosteroids. Pruritus ani, vulvae, scroti, seborrheic dermatitis, atopic eczema in children.

Paediatric information:

Although the antibiotic is indicated for ocular use in children, it is not recommended for use with a steroid combination. However, the topical ointment is authorised for atopic eczema in children.

It is however important to note that another auricular combination preparation of dexamethasone and neomycin is on the market and is indicated in children 2 years and older. The preparation is available as a spray and includes glacial acetic acid, dexamethasone and neomycin sulphate as API's but no information has been submitted by the MAH holder.

➤ **Dexamethasone + Neomycin + Polymyxin B sulphate (Alcon)**

The fixed combination was first authorised in Finland in April 1965 and is available as:

Dexamethasone 1 mg/ml, neomycin sulphate 3500 IU/ml and polymyxin B sulphate 6000 IU/ml; eye drops, suspension.

Dexamethasone 1 mg/ml, neomycin sulphate 3500 IU/ml and polymyxin B sulphate 7500 IU/ml; eye drops, solution.

Dexamethasone 1 mg/g, neomycin sulphate 3500 IU/g and polymyxin B sulphate 6000 IU/g; eye ointment.

Dexamethasone 1 mg/ml, neomycin sulphate 3500 IU/ml and polymyxin B sulphate 7500 IU/ml; ear drops, solution.

The combination is indicated for:

Eye drops/eye ointment: Steroid responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial infection or a risk of bacterial ocular infection exists (such as inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe, chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies).

Paediatric information:

This combination is indicated for use in children over 2 years of age in the following countries: Cyprus, Czech Republic, Germany, Ireland and the UK. It is also licensed for use in adolescents in Estonia, Latvia, Poland, Romania and Slovenia.

➤ **Dexamethasone isonicotinate + Tramazoline hydrochloride (Alcon)**

The fixed combination was first authorised in Germany in September 1979 and is only available in this member state. It is available as:

Dexamethasone-21-isonicotinate 0.25 mg/ml and tramazoline hydrochloride 0.632 mg/ml; eye drop suspension.

The combination is indicated for:

Non-infectious inflammatory processes including allergic conditions of the eye, eyelids, lacrimal sac and lacrimal gland. The product can also be used after eye surgery, ocular injuries and damage due to foreign bodies.

Paediatric information: Although the antibiotic is indicated for use in children, it is not recommended for use with a steroid combination.

IV. 2 Non-clinical aspects

Preclinical studies have not been provided or summarised by the MAHs on any of the dexamethasone combinations. There is no literature review conducted by Alcon but Sanofi Aventis (Dexamethasone + framycetin + gramicidin combination) have provided the information below:

➤ **Dexamethasone + framycetin + gramicidin (Sanofi)**

No nonclinical study has been conducted in juvenile animals by Sanofi-aventis. A literature review based on Medline and Embase databases has been performed and the search terms were:

- framycetin AND gramicidin AND dexamethasone, limited to animal data,

- framycetin OR gramicidin OR dexamethasone/ eye drops, ear drops, limited to animal data.

The available information was analyzed and only articles involving juvenile animals were taken into consideration.

No nonclinical safety study on the fixed-dose combination of framycetin sulphate, gramicidin and dexamethasone is available in literature.

Although scientifically interesting, these articles do not provide any new relevant information not already well-known and addressed in the European labelling texts.

IV.3 Clinical aspects

Dexamethasone + framycetin + gramicidin (Sofradex eye/ear drops)

The MAH (Sanofi - aventis) submitted an overview of four bibliographic studies and a Cochrane review with regards to the ear preparations and quoted a Cochrane review for the eye preparation. A comprehensive literature review was also submitted with regards to safety updates. No paediatric clinical trials have been performed or sponsored by the MAH. All the articles have been provided

The following 4 articles including a review were cited as of paediatric interest identified by the applicant:

- Alter SA, Vidwan NK, Sobande PO, Omoloja A, Bennett JS. **Common Childhood Bacterial Infections**. Curr Probl Pediatr Adolesc Health Care 2011;41:256-283
- Kaushik V, Malik T, Saeed SR. **Interventions for acute otitis externa**. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD004740. DOI: 10.1002/14651858.CD004740.pub2.
- Rosenfeld RM, Brown L, Cannon CR, Dolor RJ, Ganiats TG, Hanley M et al; American Academy of Otolaryngology-Head and Neck Surgery Foundation. **Clinical practice guideline: acute otitis externa**. Otolaryngol Head Neck Surg 2006; 134: S4-23
- Leach A. **Topical Ciprofloxin Versus Topical Framycetin-Gramicidin-Dexamethasone in Australian Aboriginal Children With Recently Treated Chronic Suppurative Otitis Media. A Randomized Controlled Trial**. Pediatr Infect Dis J 2008; 27: 692–698.

Two clinical studies have been published with Sofradex. The first was an open randomised blinded assessed study in 60 adults with AOE which demonstrated that a clinically highly significant improvement of symptoms between day 0 and day 10 with 2 drops administered in each ear t.d.s. for 10 days (R.B. Smith 1990). The second one was specifically based in Australia on 1 to 16 year old aboriginal children with chronic suppurative otitis media as discussed below (Leach A 2008).

The clinical overview provided covers all the indications in the current SmPC and the data reviewed confirms the efficacy and overall safety when the combination is used appropriately. . The paediatric literature review is extensive and covers both the use in ocular and auricular use. The product has been used extensively in children but is contraindicated in infants. The applicant has proposed a harmonisation of the SmPC's across Europe and the following extra warnings to be added to section 4.4 of the SmPC:

Prolonged use may lead to the risk of adrenal suppression in infants.

Aminoglycosides antibiotics may cause irreversible, partial or total deafness when given systemically or when applied topically to open wounds or damaged skin. This effect is dose related and is enhanced by renal or hepatic impairment. Although this effect has not been reported following ocular use; the possibility should be considered when high dose topical is given to small children or infants.

A clinical study (Leach A. Topical Ciprofloxin versus Topical Framycetin-Gramicidin-Dexamethasone in Australian Aboriginal Children with Recently Treated Chronic Suppurative Otitis Media. A Randomised Controlled Trial. *Pediatr Infect Dis J* 2008; 27: 692–698.) was presented from public data. The trial included 97 children however it did not show any improvement in patients with CSOM using both therapies. Side effects however were rare. This study concentrated in the type of population used and their limitations in hygiene hence there was no improvement.

A safety review was conducted and no new safety concerns were present in the paediatric population.

Dexamethasone + Tobramycin

The MAH submitted the Finnish worksharing (FI/W/002/pdWS/001) report for Tobramycin which included the following study with Tobradex (dexamethasone and tobramycin combination). No discussion in the clinical overview of the MAH was provided, however one clinical study was referred to; Clinical Evaluation of Tobradex Ophthalmic Suspension Versus Tobramycin Ophthalmic Solution (Tobrex) - (C-91-92).

Tobradex is not recommended for use in children and adolescents less than 18 years of age. Thus, no changes to the current product information are warranted.

Dexamethasone + Chloramphenicol (Alcon)

The medical literature does not support the use of dexamethasone and chloramphenicol combination products in the paediatric population.

The applicant states that there is no paediatric information available from clinical trials for any of the dexamethasone combination products and that there are no literature reports of the ocular use of dexamethasone and chloramphenicol combination products used in the paediatric population for the indications of the Alcon products. A safety profile in paediatric population was provided by the MAH and no adverse events were reported in children.

Dexamethasone + gentamycin + tetrazycline hydrochloride (Alcon)

There is no medical literature available to support the use of dexamethasone, gentamycin and tetrazycline hydrochloride combination products in the paediatric population. This combination is not indicated for the paediatric population hence there are no proposed changes to the SmPC.

Dexamethasone + neomycin sulphate (Alcon)

The topical ointment is indicated in children only for atopic eczema. Specific clinical data to support the safety and efficacy of ocular and dermatologically applied dexamethasone/neomycin in children and adolescents is not available. No SmPC changes are proposed. Specific clinical data to support paediatric ophthalmic use for the eye ointment are unavailable. The combination is not indicated for the paediatric population hence there are no proposed changes to the SmPC.

Dexamethasone + neomycin + polymyxin B sulphate (Alcon)

Alcon's dexamethasone 1 mg/ml, neomycin sulphate 3,500 I.U./ml and polymyxin B sulphate 6,000 I.U./ml and 7,500 I.U./ml eye/ear drops and eye ointment combination products are licensed for use in children (aged 2-18 years) in Cyprus, Czech Republic, Germany, Ireland, and the UK. These products are also licensed for use in adolescents in Estonia, Latvia, Poland, Romania and Slovenia. It is difficult to harmonise SmPCs across all EU countries since the safety and efficacy of the eye drops and eye ointments in children and adolescents have been established by broad clinical experience but no clinical data is available.

A safety profile in paediatric population was provided by the MAH and no serious adverse events were reported in children

Dexamethasone isonicotinate + tramazoline hydrochloride (Alcon)

The MAH's combination of dexamethasone-21-isonicotinate 0.25 mg/ml and tramazoline hydrochloride 0.632 mg/ml eye drop suspension is only approved in Germany as DEXA BICIRON® eye drops. Use in children is not listed as a specific contraindication in the SmPC; however, no recommendations or specific details relating to use in children or adolescents are listed in the current SmPC. Specific clinical data to support the indicated uses for this product in children are not available.

Tramazoline hydrochloride is a sympathomimetic agent and causes constriction of dilated arterioles in the eye. It also helps normalise any increased blood supply to mucous membranes and reduces symptoms of conjunctival irritation.

This combination is not indicated for the paediatric population hence there are no proposed changes to the SmPC. No safety data in children is available.

IV.4 Discussion on clinical aspects and conclusion

➤ Dexamethasone + framycetin + gramicidin

In the submitted articles of the clinical overview the use of the combination in children for both auricular and ocular use has been investigated. The safety and efficacy of the product's use in children has been discussed and a thorough post marketing safety update has been presented for events in the paediatric population. The indications in children are less than those proposed in adults.

The following changes to the SmPC section 4.4 are recommended as well as the inclusion of the duration of treatment in section 4.2.:

Prolonged use may lead to the risk of adrenal suppression in infants.

Aminoglycoside antibiotics may cause irreversible, partial or total deafness when given systemically or when applied topically to open wounds or damaged skin. This effect is dose related and is enhanced by renal or hepatic impairment. Although this effect has not been reported following ocular use, the possibility should be considered when high dose topical is given to small children or infants.

No changes are proposed in the rest of the combinations presented.

Member states Overall Conclusion and Recommendation

Overall conclusion

Most of the eye and ear preparations for dexamethasone combinations discussed are not indicated in children. The two combinations indicated for children have been on the market for a number of years and the overall benefit/risk ratio continues to be beneficial.

Recommendation

Dexamethasone + framycetin + gramicidin

The recommendations for changes/additions to the SmPC and PL are as follows:

SmPC Section 4.2:

Treatment duration should be short (not exceeding 7 days) (see section 4.4)

SmPC Section 4.4

Prolonged use of dexamethasone may lead to the risk of adrenal suppression in infants.

Aminoglycosides antibiotics may cause irreversible, partial or total deafness when given systemically or when applied topically to open wounds or damaged skin. This effect is dose

related and is enhanced by renal or hepatic impairment. Although this effect has not been reported following ocular use; the possibility should be considered when high dose topical is given to small children or infants.

These changes should also be incorporated in the PIL.

PIL Section 3:

Do not use “x” longer than 7 days without talking to your doctor.

A Type IB variation to be requested from the MAH within 90 days of the publication of this Public Assessment Report (PAR).

V. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

- 1) A. POTAMITIS MEDICARE LTD (62, Arch. Kyprianou Av., 2059 Strovolos, Nicosia, Cyprus)
- 2) ALCON CUSÍ, S.A. (c/Camil Fabra, 58 08320 El Masnou – Barcelona, Spain)
- 3) ALCON Laboratories (4 rue Henri Sainte-Claire Deville, 92563 RUEIL-MALMAISON Cedex, France)
- 4) ALCON Ophthalmika GmbH (Mariahilferstr. 121 b, A-1060 Vienna, Austria)
- 5) ALCON PORTUGAL Produtos e Equipamentos Oftalmológicos, Lda (Rua Castilho, 201 - 1.,1070-051 Lisboa, Portugal)
- 6) ALCON PORTUGAL - Produtos e Equipamentos Oftalmológicos, Lda. Quinta da Fonte, Edifício D. Sancho I (Piso 3, Rua dos Malhões, nº 4, 2770-071 Paço D’ Arcos, Portugal)
- 7) Alcon Bulgaria EOOD (10, Dimitar Manov str., Sofia 1408, Bulgaria)
- 8) Alcon Danmark A/S (Rødovre Parkvej 25, DK-2610 Rødovre, Denmark)
- 9) Alcon Finland Oy (Rajatorpantie 41 C, 01640 Vantaa, Finland)
- 10) Alcon Hungary Ltd (1117 Budapest, Irinyi u. 4-20., Hungary)
- 11) Alcon Laboratories UK, Ltd. (Pentagon Park, Boundary Way, Hemel Hempstead, Herts HP2 7UD, United Kingdom)
- 12) Alcon Norge AS. (Postboks 618 Skøyen, 0214 Oslo, Norway)

- 13) Alcon Pharma GmbH (Blankreutestr. 1, 79108 Freiburg, Germany)
- 14) Alcon Pharmaceuticals (Czech Republic) s.r.o. (Prague, Czech Republic)
- 15) ALCON INC HUENENBERG SWITZERLAND (Distribution in Greece: PHARMEX S.A. (132, Kifisou Ave. 12131 Peristeri, Greece)
- 16) PHARMEX S.A. (132 Kifisou Ave, 12131 Peristeri, Greece)
- 17) SA ALCON-COUVREUR NV (Rijksweg 14, 2870 PUURS, Belgium)
- 18) Sanofi Aventis Malta Ltd (Triq il-Kan. K. Pirotta, Birkirkara BKR 1114, Malta)
- 19) Sanofi-aventis (One Onslow Street, Guildford, Surrey, GU1 4YS, United Kingdom)
- 20) Sanofi-aventis Norge AS (PO Box 133, 1325 Lysaker, Norway)
- 21) sanofi-aventis Denmark A/S (Slotsmarken 13, 2970 Hørsholm, Denmark)
- 22) sanofi-aventis Ireland Ltd. (Citywest Business Campus, Dublin 24, Ireland)
- 23) sanofi-aventis Netherlands B.V. (Kampenringweg 45 D-E, 2803 PE GOUDA, The Netherlands)