SUSTAINED-RELEASE IMPLANTS FOR LOWERING INTRAOCULAR PRESSURE WITH EXTENDED DURATION OF EFFECT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/583,967 filed on November 9, 2018 and U.S. Provisional Application No. 62/683,337 filed on June 11, 2018, the entire content of which are incorporated herein by reference.

BACKGROUND

Field

The disclosure of the present application generally relates to drug delivery implants, and more specifically, drug delivery implants used to treat ocular conditions.

Description of the Related Art

Poor adherence to topical intraocular pressure (IOP)–lowering medication is common in glaucoma, associated with worse outcomes.[1] Because of these limitations, biodegradable sustained-release implant containing bimatoprost, such as those described in U.S. Patent Application Publication No. 2015-0118279, which is herein incorporated by reference in its entirety (including disclosures of formulations, implant dimensions, methods of use, and polymer compositions and properties), has developed to address nonadherence in the glaucoma population. Other bimatoprost-containing intraocular implants have been described in U.S. Patent No. 7,799,336, which is incorporated by reference in its entirety. While these publications describe implants which deliver drug to a patient's eye over an extended period of time, it is desirable to develop a drug which has an extended duration of clinical effect, for example, an implant that can reduce a patient's intraocular pressure over at least one year.

SUMMARY

In one aspect, provided herein is a use of single intraocular implant comprising bimatoprost or a salt thereof and a biodegradable polymer in the manufacture of a medicament for reducing intraocular pressure (IOP) in the eye of a patient, wherein the intraocular implant is to be injected into the anterior chamber of a patient in need thereof; and wherein the intraocular implant is effective to reduce the IOP of the patient in need thereof over a period of time between about 12 months and about 24 months.

In another aspect, provided herein is a use of one or more single intraocular implants comprising bimatoprost or a salt thereof and a biodegradable polymer in the manufacture of a

medicament for treating open angle glaucoma or ocular hypertension in a patient, wherein the one or more single intraocular implants are to be injected into the anterior chamber of the eye of a patient in need thereof at a frequency of one intraocular implant every four months to one intraocular implant every twelve months over a treatment period comprising injection of a first intraocular implant and a final intraocular implant; wherein the intraocular implants are effective to reduce the IOP of the patient in need thereof over a period of time between about 12 months and about 24 months after injection of the final intraocular implant.

In another aspect, provided herein is a use of one or more single intraocular implants comprising bimatoprost or a salt thereof and a biodegradable polymer in the manufacture of a medicament for treating open angle glaucoma or ocular hypertension in a patient, wherein the one or more single intraocular implants are to be injected at a frequency of one intraocular implant every four months to one intraocular implant every twelve months over a treatment period comprising injection of a first intraocular implant and a final intraocular implant; wherein, after injection of the final implant, the patient does not require rescue medication for a period of time between about 12 months and about 24 months after injection of the final intraocular implant.

Accordingly, an example provides a method of reducing intraocular pressure (IOP) in an eye of a patient including injecting a single intraocular implant comprising bimatoprost or a salt thereof and a biodegradable polymer into the anterior chamber of a patient in need thereof, where the intraocular implant is effective to reduce the IOP of the patient in need thereof over a period of time between about 12 months and about 24 months. In some examples, the intraocular implant is effective to reduce the IOP of the patient in need thereof of a period of time of about 24

months. In some examples the intraocular implant includes 6 μg, 10 μg, 15 μg or 20 μg of bimatoprost or a salt thereof. In an example, the intraocular implant includes a biodegradable polymer matrix, polyethylene glycol 3350, and bimatoprost or a salt thereof, wherein the bimatoprost or a salt thereof and polyethylene glycol 3350 are associated with the biodegradable polymer matrix, which includes an ester end poly(D,L-lactide) having an inherent viscosity of 0.25 dl/g to 0.35 dl/g, an acid end poly(D,L-lactide) having an inherent viscosity of 0.16 dl/g to 0.24 dl/g, and an ester end poly(D,L-lactide-co-glycolide) having an inherent viscosity of 0.16 dl/g to 0.24 dl/g and a D,L-lactide to glycolide molar ratio of about 75:25, wherein the bimatoprost or a salt thereof constitutes 18% to 22% of the implant by weight, the ester end poly(D,L-lactide) constitutes 18% to 22% of the implant by weight, the acid end poly(D,L-lactide) constitutes 13.5% to 16.5% of the implant by weight, the ester end poly(D,L-lactide-co-glycolide) constitutes 36% to 44% of the implant by weight, and wherein the polyethylene glycol 3350 constitutes 3.5% to 6.5% of the implant by weight, wherein the inherent viscosity of each of the poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) polymers is determined for a 0.1% solution of the polymer in chloroform at 25°C.

In an example, a method of treating open angle glaucoma or ocular hypertension in a patient includes injecting one or more intraocular implants comprising bimatoprost or a salt thereof and a biodegradable polymer into the anterior chamber of the eye of a patient in need thereof at a frequency of one intraocular implant every four months to one intraocular implant every twelve months over a treatment period including injection of a first intraocular implant and a final intraocular implant. The intraocular implants can be effective to reduce the IOP of the patient in need thereof over a period of time between about 12 months and about 24 months after injection of the final intraocular implant. According to some examples, the patient receives one intraocular implant every four months, and the intraocular implant or implants are effective to reduce the IOP of the patient in need thereof over a period of time between about 12 months and about 24 months. In an example, the patient receives between two implants and eight implants over the treatment period. In some examples, the patient receives three implants. According to other examples, the intraocular implants are effective to reduce the IOP of the patient in need thereof over a period of time of about 12 months. The intraocular implant can include 6 μg, 10 μg, 15 μg of bimatoprost or a salt thereof. In an example, the intraocular implant includes a biodegradable polymer matrix, polyethylene glycol 3350, and bimatoprost or a salt thereof,

wherein the bimatoprost or a salt thereof and polyethylene glycol 3350 are associated with the biodegradable polymer matrix, which includes an ester end poly(D,L-lactide) having an inherent viscosity of 0.25 dl/g to 0.35 dl/g, an acid end poly(D,L-lactide) having an inherent viscosity of 0.16 dl/g to 0.24 dl/g, and an ester end poly(D,L-lactide-co-glycolide) having an inherent viscosity of 0.16 dl/g to 0.24 dl/g and a D,L-lactide to glycolide molar ratio of about 75:25, wherein the bimatoprost or a salt thereof constitutes 18% to 22% of the implant by weight, the ester end poly(D,L-lactide) constitutes 18% to 22% of the implant by weight, the acid end poly(D,L-lactide) constitutes 13.5% to 16.5% of the implant by weight, the ester end poly(D,L-lactide-co-glycolide) constitutes 36% to 44% of the implant by weight, and wherein the polyethylene glycol 3350 constitutes 3.5% to 6.5% of the implant by weight, wherein the inherent viscosity of each of the poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) polymers is determined for a 0.1% solution of the polymer in chloroform at 25°C.

According to some examples, a method of treating open angle glaucoma or ocular hypertension in a patient includes injecting one or more single intraocular implants that include bimatoprost or a salt thereof and a biodegradable polymer into the anterior chamber of the eye of a patient in need thereof at a frequency of one intraocular implant every four months to one intraocular implant every twelve months over a treatment period including injection of a first intraocular implant and a final intraocular implant. In such examples, after injection of the final implant, the patient does not require rescue medication for a period of time between about 12 months and about 24 months. In some examples, the patient receives one intraocular implant every four months and the patient does not require rescue medication over a period of time between about 12 months and about 24 months after injection of the final implant. According to some examples, the patient receives between two implants and eight implants over the treatment period. The patient can receive three implants. In an example, the patient does not require rescue medication over a period of time of about 12 months. The intraocular implant can include, in some examples, 6 μg, 10 μg, or 15 μg of bimatoprost or a salt thereof. In an example, the intraocular implant includes a biodegradable polymer matrix, polyethylene glycol 3350, and bimatoprost or a salt thereof, wherein the bimatoprost or a salt thereof and polyethylene glycol 3350 are associated with the biodegradable polymer matrix, which includes an ester end poly(D,L-lactide) having an inherent viscosity of 0.25 dl/g to 0.35 dl/g, an acid end poly(D,L-lactide) having an inherent viscosity of 0.16 dl/g to 0.24 dl/g, and an ester end poly(D,L-lactide-co-glycolide) having an inherent viscosity of 0.16 dl/g to 0.24 dl/g and a D,L-lactide to glycolide molar ratio of

about 75:25, wherein the bimatoprost or a salt thereof constitutes 18% to 22% of the implant by weight, the ester end poly(D,L-lactide) constitutes 18% to 22% of the implant by weight, the acid end poly(D,L-lactide) constitutes 13.5% to 16.5% of the implant by weight, the ester end poly(D,L-lactide-co-glycolide) constitutes 36% to 44% of the implant by weight, and wherein the polyethylene glycol 3350 constitutes 3.5% to 6.5% of the implant by weight, wherein the inherent viscosity of each of the poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) polymers is determined for a 0.1% solution of the polymer in chloroform at 25°C. According to some examples of the method, the rescue medication includes eye drops containing a prostaglandin analog or prostamide. In some examples, the method is effective to reduce the IOP of the patient in need thereof by about 30% from baseline.

BRIEF DESCRIPTION OF THE FIGURES

These and other features will now be described with reference to the drawings summarized below. These drawings and the associated description are provided to illustrate one or more embodiments and not to limit the scope of the invention.

Figure 1 illustrates a clinical study dosing design, according to example embodiments including the study design described in EXAMPLE 2.

Figure 2 shows the baseline to week 12 mean IOP reduction results comparing formulations described herein compared to topical administration of timolol solution according to the methods described in EXAMPLE 2.

Figure 3 shows the mean difference in IOP values at weeks 2, 6 and 12 within a treatment cycle according to the methods described in EXAMPLE 2.

Figure 4 shows the use of rescue medication after third cycle administration, according to example administration methods disclosed herein, comparing implant formulations described herein containing 10 μg or 15 μg against timolol solution applied twice a day according to the methods described in EXAMPLE 2.

DESCRIPTION

Definitions

WHAT IS CLAIMED IS:

1. Use of single intraocular implant comprising bimatoprost or a salt thereof and a biodegradable polymer in the manufacture of a medicament for reducing intraocular pressure (IOP) in the eye of a patient,

wherein the intraocular implant is to be injected into the anterior chamber of a patient in need thereof; and

wherein the intraocular implant is effective to reduce the IOP of the patient in need thereof over a period of time between about 12 months and about 24 months.

2. The use of claim 1, wherein the intraocular implant is effective to reduce the IOP of the patient in need thereof of a period of time of about 24 months.

3. The use of claim 1 or claim 2, wherein the intraocular implant comprises 6 μg, 10 μg, 15 μg or 20 μg of bimatoprost or a salt thereof.

4. The use of any one of claims 1-3, wherein the intraocular implant comprises a biodegradable polymer matrix, polyethylene glycol 3350, and bimatoprost or a salt thereof, wherein the bimatoprost or a salt thereof and polyethylene glycol 3350 are associated with the biodegradable polymer matrix, which comprises

   a) an ester end poly(D,L-lactide) having an inherent viscosity of 0.25-0.35 dl/g,
   b) an acid end poly(D,L-lactide) having an inherent viscosity of 0.16-0.24 dl/g, and
   c) an ester end poly(D,L-lactide-co-glycolide) having an inherent viscosity of 0.16-0.24 dl/g and a D,L-lactide to glycolide molar ratio of about 75:25;

wherein the bimatoprost or a salt thereof constitutes 18 to 22% of the implant by weight, the ester end poly(D,L-lactide) constitutes 18 to 22% of the implant by weight, the acid end poly(D,L-lactide) constitutes 13.5 to 16.5% of the implant by weight, the ester end poly(D,L-lactide-co-glycolide) constitutes 36 to 44% of the implant by weight, and wherein the polyethylene glycol 3350 constitutes 3.5 to 6.5% of the implant by weight, wherein the inherent viscosity of each of the poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) polymers is determined for a 0.1% solution of the polymer in chloroform at 25°C.

5. Use of one or more single intraocular implants comprising bimatoprost or a salt thereof and a biodegradable polymer in the manufacture of a medicament for treating open angle glaucoma or ocular hypertension in a patient,

wherein the one or more single intraocular implants are to be injected into the anterior chamber of the eye of a patient in need thereof at a frequency of one intraocular implant every four months to one intraocular implant every twelve months over a treatment period comprising injection of a first intraocular implant and a final intraocular implant;

wherein the intraocular implants are effective to reduce the IOP of the patient in need thereof over a period of time between about 12 months and about 24 months after injection of the final intraocular implant.

6. The use of claim 5, wherein the patient is to receive one intraocular implant every four months; and wherein the intraocular implants are effective to reduce the IOP of the patient in need thereof over a period of time between about 12 months and about 24 months.

7. The use of claim 5 or claim 6 wherein the patient is to receive between two implants and eight implants over the treatment period.

8. The use of any one of claims 5 – 6 wherein the patient is to receive three implants.

9. The use of any one of claims 5-8 wherein the intraocular implants are effective to reduce the IOP of the patient in need thereof over a period of time of about 12 months.

10. The use of any one of claims 5-9, wherein the intraocular implant comprises 6 μg, 10 μg, 15 μg, or 20 μg of bimatoprost or a salt thereof.

11. The use of any one of claims 5-10, wherein the intraocular implant comprises a biodegradable polymer matrix, polyethylene glycol 3350, and bimatoprost or a salt thereof, wherein the bimatoprost or a salt thereof and polyethylene glycol 3350 are associated with the biodegradable polymer matrix, which comprises

d) an ester end poly(D,L-lactide) having an inherent viscosity of 0.25-0.35 dl/g,

e) an acid end poly(D,L-lactide) having an inherent viscosity of 0.16-0.24 dl/g, and

f) an ester end poly(D,L-lactide-co-glycolide) having an inherent viscosity of 0.16-0.24 dl/g and a D,L-lactide to glycolide molar ratio of about 75:25;

wherein the bimatoprost or a salt thereof constitutes 18 to 22% of the implant by weight, the ester end poly(D,L-lactide) constitutes 18 to 22% of the implant by weight, the acid end poly(D,L-lactide) constitutes 13.5 to 16.5% of the implant by weight, the ester end poly(D,L-lactide-co-glycolide) constitutes 36 to 44% of the implant by weight, and wherein the polyethylene glycol 3350 constitutes 3.5 to 6.5% of the implant by weight, wherein the inherent viscosity of each of the poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) polymers is determined for a 0.1% solution of the polymer in chloroform at 25°C.

12. The use of any one of claims 5-11, wherein the intraocular implants are effective to reduce the IOP of the patient in need thereof by about 30% from baseline.

13. Use of one or more single intraocular implants comprising bimatoprost or a salt thereof and a biodegradable polymer in the manufacture of a medicament for treating open angle glaucoma or ocular hypertension in a patient,

wherein the one or more single intraocular implants are to be injected at a frequency of one intraocular implant every four months to one intraocular implant every twelve months over a treatment period comprising injection of a first intraocular implant and a final intraocular implant;

wherein, after injection of the final implant, the patient does not require rescue medication for a period of time between about 12 months and about 24 months after injection of the final intraocular implant.

14. The use of claim 13, wherein the patient is to receive one intraocular implant every four months; and wherein the patient does not require rescue medication over a period of time between about 12 months and about 24 months after injection of the final implant.

15. The use of claim 13 or claim 14 wherein the patient is to receive between two implants and eight implants over the treatment period.

16. The use of any one of claims 13 – 15 wherein the patient is to receive three implants.

17. The use of any one of claims 13-16 wherein the patient does not require rescue medication over a period of time of about 12 months.

18. The use of any one of claims 13-17, wherein the intraocular implant comprises 10 μg, 15 μg of bimatoprost or a salt thereof.

19. The use of any one of claims 13-18, wherein the intraocular implant comprises a biodegradable polymer matrix, polyethylene glycol 3350, and bimatoprost or a salt thereof, wherein the bimatoprost or a salt thereof and polyethylene glycol 3350 are associated with the biodegradable polymer matrix, which comprises

    g) an ester end poly(D,L-lactide) having an inherent viscosity of 0.25-0.35 dl/g,
    h) an acid end poly(D,L-lactide) having an inherent viscosity of 0.16-0.24 dl/g, and
    i) an ester end poly(D,L-lactide-co-glycolide) having an inherent viscosity of 0.16-0.24 dl/g and a D,L-lactide to glycolide molar ratio of about 75:25;

wherein the bimatoprost or a salt thereof constitutes 18 to 22% of the implant by weight, the ester end poly(D,L-lactide) constitutes 18 to 22% of the implant by weight, the acid end poly(D,L-lactide) constitutes 13.5 to 16.5% of the implant by weight, the ester end poly(D,L-lactide-co-glycolide) constitutes 36 to 44% of the implant by weight, and wherein the polyethylene glycol 3350 constitutes 3.5 to 6.5% of the implant by weight, wherein the inherent viscosity of each of the poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) polymers is determined for a 0.1% solution of the polymer in chloroform at 25°C.

20. The use of any one of claims 13 – 19, wherein the rescue medication comprises eye drops containing a prostaglandin analog or prostamide.

21. The use of any one of claims 13-20, wherein the intraocular implants are effective to reduce the IOP of the patient in need thereof by about 30% from baseline.