(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 124 945 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
20.04.2011 Bulletin 2011/16

(21) Application number: **07865831.7**

(22) Date of filing: **18.12.2007**

(51) Int Cl.:
A61K 31/4412 *(2006.01)*

(86) International application number:
PCT/US2007/087988

(87) International publication number:
WO 2008/077068 (26.06.2008 Gazette 2008/26)

(54) METHOD OF PROVIDING PIRFENIDONE THERAPY TO A PATIENT

VERFAHREN ZUR BEREITSTELLUNG EINER PIRFENIDONTHERAPIE AN EINEM PATIENTEN

PROCÉDÉ PERMETTANT D'ADMINISTRER UNE THÉRAPIE PAR LE PIRFENIDONE À UN PATIENT

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR

(30) Priority: **18.12.2006 US 870593 P**

(43) Date of publication of application:
02.12.2009 Bulletin 2009/49

(73) Proprietor: **Intermune, Inc.**
Brisbane, CA 94005-1021 (US)

(72) Inventor: **BRADFORD, Williamson Ziegler**
Ross, CA 94957 (US)

(74) Representative: **Pilkington, Stephanie Joan**
Potter Clarkson LLP
Park View House
58 The Ropewalk
Nottingham
NG1 5DD (GB)

(56) References cited:
WO-A-2007/064738

- **BABOVIC-VUKSANOVIC D ET AL: "Phase II trial of pirfenidone in adults with neurofibromatosis type 1." NEUROLOGY 28 NOV 2006, vol. 67, no. 10, 28 November 2006 (2006-11-28), pages 1860-1862, XP002476128 ISSN: 1526-632X**
- **AZUMA ARATA ET AL: "Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis." AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE 1 MAY 2005, vol. 171, no. 9, 1 May 2005 (2005-05-01), pages 1040-1047, XP002476129 ISSN: 1073-449X cited in the application**
- **BOWEN JAMES D ET AL: "Open-label study of pirfenidone in patients with progressive forms of multiple sclerosis." MULTIPLE SCLEROSIS, vol. 9, no. 3, June 2003 (2003-06), pages 280-283, XP009098524 ISSN: 1352-4585**
- **RAGHU GANESH ET AL: "Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: Results of a prospective, open-label phase II study", AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, vol. 159, no. 4 PART 1, April 1999 (1999-04), pages 1061-1069, ISSN: 1073-449X**
- **RAGHU GANESH ET AL: "Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: Results of a prospective, open-label phase II study" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, vol. 159, no. 4 PART 1, April 1999 (1999-04), pages 1061-1069, ISSN: 1073-449X**

EP 2 124 945 B1

Description

BACKGROUND

Field of the Invention

[0001] The invention relates to methods for decreasing adverse events associated with pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) therapy.

Description of the Related Art

[0002] Pirfenidone is small drug molecule whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. It is a non-peptide synthetic molecule with a molecular weight of 185.23 Daltons. Its chemical elements are expressed as $C_{12}H_{11}NO$, and its structure and synthesis are known. Pirfenidone is manufactured commercially and being evaluated clinically as a broad-spectrum antifibrotic drug. Several pirfenidone investigational New Drug Applications (INDs) are currently on file with the U.S. Food and Drug Administration. Phase II human investigations are ongoing or have recently been completed for pulmonary fibrosis, renal glomerulosclerosis, and liver cirrhosis. There have been other Phase II studies that used pirfenidone to treat benign prostate hypertrophy, hypertrophic scarring (keloids), and rheumatoid arthritis.

[0003] Pirfenidone is being investigated for therapeutic benefits to patients suffering from fibrosis conditions such as Hermansky-Pudlak Syndrome (BPS) associated pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF). Pirfenidone is also being investigated for a pharmacologic ability to prevent or remove excessive scar tissue found in fibrosis associated with injured tissues including that of lungs, skin, joints, kidneys, prostate glands, and livers. Published and unpublished basic and clinical research suggests that pirfenidone may safely slow or inhibit the progressive enlargement of fibrotic lesions, and prevent formation of new fibrotic lesions following tissue injuries.

[0004] It is understood that one mechanism by which pirfenidone exerts its therapeutic effects is modulating cytokine actions. Pirfenidone is a potent inhibitor of fibrogenic cytokines and TNF-α. It is well documented that pirfenidone inhibits, excessive biosynthesis or release of various fibrogenic cytokines such as TGF-β1, bFGF, PDGF, and EGF. Zhang S et al., Australian and New England J Ophthalmology 26:S74-S76 (1998). Experimental reports also show that pirfenidone blocks the synthesis and release of excessive amounts of TNF-α from macrophages and other cells. Cain et al., Int'l J Immunopharmacology 20:685-695 (1998).

[0005] As an investigational drug, pirfenidone is provided in tablet and capsule forms principally for oral administration. Various formulations have been tested and adopted in clinical trials and other research and experiments. The most common adverse reactions or events associated with pirfenidone therapy include gastrointestinal upset, nausea, fatigue, somnolence, dizziness, headache, and photosensitivity rash. Many of these effects can interfere with everyday activities and quality of life. These effects appear to be dose related. The adverse reactions associated with pirfenidone therapy are exacerbated when pirfenidone is administered at these higher doses.

[0006] Currently, adverse events following administration of pirfenidone are alleviated by dose reduction or discontinuation of pirfenidone. In a recent study, for adverse events rated Grade 2 or worse, the dosage was reduced in a stepwise manner: from 9 tablets having 200 mg of pirfenidone per day to 6 tablets having 200 mg of pirfenidone per day and 6 tablets having 200 mg of pirfenidone per day to 3 tablets having 200 mg of pirfenidone per day. Azuma, A. et al., Am J Respir Crit Care Med 171:1040-47 (2005) ("Azuma study"). More specifically, if, after a period of 14 days of observation with reduced dosage, the adverse event persisted or increased, the dosage was further reduced by one more step-from 6 tablets per day to 3 tablets per day. If the adverse event persisted or increased despite reducing the dosage to 3 tablets per day, the study medication was discontinued.

[0007] The Azuma study discloses a dose-titration schedule for all patients wherein patients received a 200-mg dose of pirfenidone three times a day for the first two days; then a 400-mg dose of pirfenidone three times a day for the following two days; and then a maximum 600-mg dose of pirfenidone three times a day for the remainder of treatment. Thus, the maximum dose obtained by the Azuma study was only 1,800 mg/day of pirfenidone. Additionally, the dose-titration schedule of the Azuma study reaches the full maximum dosage of pirfenidone after only four days of treatment. There is significant reason to believe that the Azuma dose escalation does not optimally match the rate of dose escalation with the rate at which a patient develops sufficient tolerance to reduce the incidence of adverse events. Thus, there remains an unmet clinical need for a method of administering higher doses of pirfenidone to a patient in a manner that eliminates or minimizes adverse events, such as nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, somnolence, and other undesirable side effects.

SUMMARY

[0008] The present invention overcomes the unmet clinical need by providing an improved, optimized dose escalation scheme for the administration of pirfenidone. The dose escalation scheme of the present invention provides pirfenidone in an amount such that the full maximum dosage is not reached for at least one week. The full maximum dosage, of pirfenidone is not reached until about Day 15 of treatment in the present invention. The present invention allows for a maximum dosage of 2,403 mg of pirfenidone per day to be administered to a patient

and also reduces the incidence of adverse events associated with the administration of pirfenidone by more accurately matching dose escalation with tolerance development in the patient. Indeed, it has been observed that even as the dosage escalates using the dosing escalation scheme described herein, adverse events, such as somnolence, decrease.

[0009] The present invention provides Pirfenidone, in an initial dose escalation regimen, for use in treating idiopathic pulmonary fibrosis (IPF), wherein the pirfenidone is for:

administering to a patient a first oral daily dosage of 801 mg as one capsule comprising 267-mg of pirfenidone three times a day for days one to seven of the dose escalation regimen;
administering to the patient a second oral daily dosage of 1602 mg as two capsules comprising 267-mg of pirfenidone three times a day for days eight to fourteen of the dose escalation regimen; and
administering to the patient a third oral daily dosage of 2403 mg as three capsules comprising 267-mg of pirfenidone three times a day for at least day fifteen of the dose escalation regimen; and
wherein said dosages are for taking with food.

[0010] The present invention also provides for the use of pirfenidone in the manufacture of a medicament for treating idiopathic pulmonary fibrosis (iPF), wherein the medicament is for:

administering to a patient a first oral daily dosage of 801 mg as one capsule comprising 267-mg of pirfenidone three times a day for days one to seven of a dose escalation regimen;
administering to the patient a second oral daily dosage of 1602 mg as two capsules comprising 267-mg of pirfenidone three times a day for days eight to fourteen of the dose escalation regimen; and
administering to the patient a third oral daily dosage of 2403 mg as three capsules comprising 267-mg of pirfenidone three times a day for at least day fifteen of the dose escalation regimen; and
wherein said dosages are for taking with food.

[0011] In an embodiment of the pirfenidone or use of the invention, the initial dose escalation regimen reduces the incidence of an adverse event associated with the administration of pirfenidone.

[0012] The present invention further provides a starter pack comprising:

a first set of compartments each having a first dosage amount of pirfenidone that is 801 mg per day as one Pill comprising 267-mg of pirfenidone three times a day; and
a second set of compartments each having a second dosage amount of pirfenidone that is 1602 mg per day as two pills comprising 267-mg of pirfenidone three times a day; and at least one additional set of compartments each having a third dosage amount of pirfenidone that is 2403 mg as three pills comprising 267-mg of pirfenidone three times a day,
wherein the first set of compartments are for administering the first dosage amount of pirfenidone for Days 1, 2, 3, 4, 5, 6 and 7, and wherein the second set of compartments are for administering a second dosage amount of pirfenidone for Days 8, 9, 10, 11, 12, 13 and 14, and wherein the additional set of compartments are for administering a third dosage amount of pirfenidone beginning on Day 15.

[0013] Thus, the present invention discloses a starter pack comprising dosage amounts of pirfenidone and compartments that separate the dosage amounts according to a daily dosage of pirfenidone. Advantageously, the compartments can be arranged in columns and in rows, although other arrangements are also contemplated.

[0014] The starter pack may comprise rows designating Day numbers and separate columns for the number of times a dosage of pirfenidone is taken each day. The starter pack may comprise, separate rows for Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 with three separate columns for three dosage amounts to be taken each day. Each of the three comportments for Days 1, 2, 3, 4, 5, 6, and 7 may separately contain one pill of 267-mag pirfenidone and each of the three compartments for Days 8, 9, 10, 11, 12, 13, and 14 may separately contain two pills of 267-mg pirfenidone. Each week of treatment may be designated on a separate panel. Each panel contained within the starter pack may be approximately the same size. The starter pack may have compartments arranged such that a user of the starter pack may administer the pirfenidone in accordance with the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Fig. 1 shows a structure of a portion of a starter pack for the first week of treatment.

[0016] Fig. 2 shows a structure of a portion of a starter pack for the second week of treatment.

[0017] Fig. 3 shows a structure of a portion of a starter pack for the third week of treatment.

[0018] Fig. 4 shows a starter pack having multiple panels that are folded.

[0019] Fig. 5 shows a starter pack having multiple panels in an unfolded position.

[0020] Fig. 6 shows another structure of a portion of a starter pack for the first week of treatment.

[0021] Fig. 7 shows another structure of a portion of a starter pack for the second week of treatment.

[0022] Fig. 8 shows another structure of a portion of a starter pack for the third week of treatment.

[0023] Fig. 9 shows a starter pack having a casing material holding three different containers in such a manner

that a user can easily slide a container out of the casing material.

[0024] Fig. 10 shows a starter pack wherein a container is partially pulled out from the casing material.

[0025] Fig. 11 shows a container comprising a panel having a plurality of compartments for containing a dosage amount of pirfenidone.

[0026] Fig. 12 shows a container wherein the panel has been pulled outside of the container.

[0027] Fig. 13 shows a starter pack having a casing material holding at least one circular panel containing pirfenidone.

[0028] Fig. 14 shows another structure of a portion of a circular starter pack for the first week of treatment.

[0029] Fig. 15 shows another structure of a portion of a circular starter pack for the second week of treatment.

[0030] Fig. 16 shows another structure of a portion of a circular starter pack for the third week of treatment.

DETAILED DESCRIPTION

[0031] The present invention discloses the use of pirfenidone in an escalating dosage regimen that mitigates adverse events associated with the use of pirfenidone and, it is believed, better matches die development of tolerance to potentially adverse effects of the drug with increases in the dosage. The escalating dosage regimen of the invention is as specified in the claims.

[0032] The third and daily dosage may be for administration on day 15 to an unlimited number of days. Preferably, the final period of time will be however long the duration of treatment with pirfenidone should last.

[0033] Thus, the present invention provides pirfenidone for use in treating IPF comprising providing an initial daily dosage of pirfenidone to the patient in an amount of 801 mg/day over the course of Day 1 to Day 7; providing a second daily dosage of pirfenidone to the patient in an amount of 1602 mg/day over the course of Day 8 to Day 14; and providing a final daily dosage of pirfenidone to the patient in an amount of 2403 mg/day on the beginning of Day 15 and continuing with the 2403 mg/day dosage on each day following Day 15.

[0034] The patient is provided one capsule (a sub-daily dosage) comprising 257-mg of pirfenidone three times a day over the course of Day 1 to Day 7, to provide a daily dosage of 801 mg pirfenidone; then the patient is provided two capsules (a sub-daily dosage) comprising 267-mg of pirfenidone three times a day over the course of Day 8 to Day 14, to provide a daily dosage of 1602 mg pirfenidone; and then the patient is provided three capsules (a sub-daily dosage) comprising 267-mg of pirfenidone three times a day on Day 15 and each day thereafter, to provide a daily dosage of 2403 mg pirfenidone where the therapy continues after Day 15.

[0035] The pirfenidone is taken with food. Thus, the patient is instructed to administer the dosage of pirfenidone with food.

[0036] The invention further provides a starter pack comprising pirfenidone. Starter packs are a relatively easy method for singulating, transporting, storing and finally dispensing oral solid drugs. Such packs include, for instance, a planar transparent piece of plastic provided with "blisters" or convex protrusions configured in rows and columns. Each of the blisters or convex protrusions is sized to receive a singulated dosage amount of the particular oral solid drug being dispensed.

[0037] Typically, at least one backing layer is fastened to a solid receiving side of the blister pack. This layer is a low strength retaining barrier. This low strength retaining layer stretches across the backs of the blisters and retains the singulated oral dosage amounts individually sealed within each of the blisters.

[0038] Dispensing of drugs from such blister packs is easy to understand. The consumer presses down on a blister from the convex side of the blister. Such pressure bears directly against the singulated oral dosage amount contained in the blister. The singulated oral solid drug is then forced through the low strength retaining barrier. This low strength retaining barrier at least partially tears and breaks away. During this partial breaking and tearing away, the singulated oral dosage amount is partially--but typically not totally-ejected from its individual blister. Preferably, it is during this partial ejection that the oral solid drug is grasped by the user and consumed as directed. The result is a safe, sterile dispensing of the drug in desired single dosage amounts from the blister pack.

[0039] The starter pack of the present invention may comprise various dosage amounts of pirfenidone designated within blisters or other individual compartments so that the patient will take the proper dosage amount of the drug each day. The starter pack may comprise many different forms. One embodiment of the starter pack is shown in Figures 1-3. Figure 1 shows a portion of a starter pack comprising dosage amounts for the first week of therapy using pirfenidone. The starter pack (10) for the first week of treatment may comprise a panel (12) having a plurality of compartments (16) for containing a dosage amount (18) of pirfenidone. The compartments (16) may be arranged in column and row fashion as illustrated, although other arrangements are also contemplated, including having all of the compartments arranged in a line, or having them arranged in a circular fashion. In an embodiment where the starter pack comprises columns and rows, each daily dosage may be represented in a singular row or a singular column.

[0040] Figure 2 shows a portion of a starter pack comprising dosage amounts for the second week of therapy using pirfenidone. The starter pack (20) for the second week of treatment may comprise a panel (22) having a plurality of compartments (26) for containing a dosage amount (28) of pirfenidone. The compartments (26) for the second week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (16) for the first week of treatment. The dosage amount (28) of pirfenidone for the second week may be greater than the dosage amount (18) of the first week.

[0041] Figure 3 shows a portion of a starter pack comprising dosage amounts for the third week of therapy using pirfenidone. The starter pack (30) for the third week of treatment may comprise a panel (32) having a plurality of compartments (36) for containing a dosage amount (38) of pirfenidone. The compartments (36) for the third week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (26) for the second week of treatment. The dosage amount (38) of pirfenidone for the third week may be greater than the dosage amount (28) of the second week.

[0042] Although Figures 1-3 show a starter pack wherein a panel represents one week of dosages, it is contemplated that a panel may be constructed to comprise more or less compartments. For instance, a panel may be constructed to hold dosage amounts for three days of treatment. In another embodiment, a panel may be constructed to hold dosage amounts for six days of treatment. In another embodiment, a panel may be constructed to hold dosage amounts for ten days of treatment. Any number of days and dosages in a single panel are contemplated by the inventors. Preferably, the starter pack may be designed so that the user administers pirfenidone according to the dose escalation scheme of the present invention.

[0043] In one embodiment, the starter pack comprises panels giving dosage amounts of pirfenidone for the first week of treatment and the second week of treatment. In another embodiment, the starter pack further comprises a panel giving dosage amounts of pirfenidone for the third week of treatment. In another embodiment, the starter pack comprises a panel or an insert that gives instructions to a patient for administering the proper dosage amount of pirfenidone.

[0044] In one embodiment, the starter pack may comprise only dosage amounts for the first week of treatment and the second week of treatment. Preferably, such a starter pack may also comprise instructions to the patient for administering the pirfenidone from a bottle for therapy after dose escalation is completed. It is contemplated that the user of the starter pack will continue therapy with pirfenidone pills from a bottle after dose escalation is completed.

[0045] The size of the starter pack and the panels that comprise the starter pack may be typical of similar starter packs already known. In a preferred embodiment, each panel within a starter pack is approximately of similar size dimensions as the other panels of the starter pack.

[0046] In some embodiments, the starter pack comprises a unitary structure, wherein the unitary structure comprises more than one panel and each panel may comprise dosage amounts for one week of treatment. In some embodiments, the starter pack comprises a panel that has printed instructions thereon. Figure 4 shows a starter pack (40) having multiple panels (42, 44, 46) that are folded. The starter pack has at least one region (48) capable of folding so that the separate panels (42, 44, 46) can be stacked upon one another while the starter pack (40) maintains its unitary structure. In some embodiments, the starter pack may comprise panels (42, 44) having compartments for containing dosages of pirfenidone. The dosages may be pushed through the low strength retaining barrier at points (45) opposite the location of the blisters.

[0047] Figure 5 shows a fully unfolded starter pack (50) comprising four panels (52, 54, 56, 58). The Week_1 panel (54) may have compartments (54a) that comprise a dosage amount (54b) of pirfenidone related to the first week of treatment. The Week 2 panel (56) may have compartments (56a) that comprise a dosage amount (56b) of pirfenidone related to the second week of treatment. Optionally, a panel for the dosage amounts of Week 3 may be included. The Week 3 panel (58) may have compartments (58a) that comprise a dosage amount (58b) of pirfenidone related to the third week of usage. The other panel (52) may be left blank or provided with instructions or any other type of indicia. In some embodiments, the starter pack (50) may comprise an adhesive seal or a sticker that holds the starter pack in folded form until the adhesive seal or sticker is broken by a user. The starter pack may comprise regions (55) capable of folding so that the separate panels (52, 54, 56, 58) can be stacked upon one another while the starter pack (50) maintains its unitary structure.

[0048] In one embodiment, one panel (54) may comprise compartments (54a) giving the dosage amount (54b) for Days 1-7 of the dose escalation scheme and the second panel (56) may comprise compartments (56a) giving the dosage amount (56b) for Days 8-14 of the dose escalation scheme. In another embodiment, an optional third panel (58) may be further provided to comprise compartments (58a) giving the dosage amount (58b) for Days 15-21 of the dose escalation scheme.

[0049] Figure 6 shows a portion of another starter pack comprising dosage amounts for the first week of therapy using pirfenidone. The starter pack (60) for the first week of treatment may comprise a panel (62) having a plurality of compartments (66) for containing a dosage amount (68) of pirfenidone. The compartments (66) may be arranged in column and row fashion as illustrated, although other arrangements are also contemplated, including having all of the compartments arranged in a line, or having them arranged in a circular fashion. Additionally, instructions may be provided on the starter pack (60) indicating the proper day and time the dosage amount (68) should be administered.

[0050] Figure 7 shows a portion of another starter pack comprising dosage amounts for the second week of therapy using pirfenidone. The starter pack (70) for the second week of treatment may comprise a panel (72) having a plurality of compartments (76) for containing a dosage amount (78) of pirfenidone. The compartments (76) for the second week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (66) for the first week of treatment. The dosage amount (78) of pirfenidone for the second week may be greater

than the dosage amount (68) of the first week. Additionally, instructions may be provided on the starter pack (70) indicating the proper day and time the dosage amount (78) should be administered.

[0051] Figure 8 shows a portion of another starter pack comprising dosage amounts for the third week of therapy using pirfenidone. The starter pack (80) for the third week of treatment may comprise a panel (82) having a plurality of compartments (86) for containing a dosage amount (88) of pirfenidone. The compartments (86) for the third week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (76) for the second week of treatment. The dosage amount (88) of pirfenidone for the third week may be greater than the dosage amount (78) of the second week. Additionally, instructions may be provided on the starter pack (80) indicating the proper day and time the dosage amount (88) should be administered.

[0052] In some embodiments, the starter pack may comprise a casing material that holds separate panels, wherein at least one panel comprises a plurality of compartments for containing a dosage amount of pirfenidone. In some embodiments, the panel may be located within a container having flat outer surfaces so that the container may easily be slid in and out of the casing material. Figure 9 shows a starter pack (90) having a casing material (98) holding three different containers (92, 94, 96) in such a manner that a user can easily slide a container out of the casing material (98). In one embodiment, each container may comprise a panel that comprises a plurality of compartments that hold a dosage amount of pirfenidone. In some embodiments, the panels may further comprise instructions or indicia so that a user can administer pirfenidone according to the dose escalation scheme. In some embodiments, a panel may be provided separately for providing indicia or instructions on using the drug. In some embodiments, indicia or instructions may be provided on one or more of the containers (92, 94, 96).

[0053] Figure 10 shows a starter pack (100) comprising a casing material (108) and at least one container (102). The container (102) is partially pulled out from the casing material (108) and may comprise a panel having a plurality of compartments for containing a dosage amount of pirfenidone. For example, the container (102) may comprise any of the panels shown in Figures 1-3 and Figures 6-8. Preferably, each panel will be approximately the same size for easy and compact insertion into the casing material (108).

[0054] Figure 11 shows a container (110) comprising a panel (112) having a plurality of compartments (116) for containing a dosage amount (118) of pirfenidone. The panel (112) is partially pulled out from the container (110) and can be slid in and out for easy use. Figure 12 shows a container (120) wherein the panel (122) having a plurality of compartments (126) for containing a dosage amount (128) of pirfenidone has been completely pulled from the container (120). Instructions may be provided on a separate sheet (124) within the container (120) in addition to the panel (122). Alternatively, instructions or other indicia may be printed directly on the container (120) or the panel (122).

[0055] One embodiment of the present invention is a starter pack comprising dosage amounts of pirfenidone and compartments that separate the dosage amounts according to a daily dosage of pirfenidone. In one embodiment, the starter pack comprises a row designating Day numbers and separate columns for the number of times a dosage of pirfenidone is taken each day. In one embodiment, the starter pack may comprise separate rows for Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 with three separate columns for three dosage amounts to be taken each day. In one embodiment, each of the three compartments for Days 1, 2, 3, 4, 5, 6, and 7 separately contain one pill of 267-mg pirfenidone and each of the three compartments for Days 8, 9, 10, 11, 12, 13, and 14 separately contain two pills of 267-mg pirfenidone. In another embodiment, each week of treatment may be designated on a separate panel. In another embodiment, each panel contained within the starter pack may be approximately the same size. In another embodiment, the starter pack has compartments arranged such that a user of the starter pack will administer the pirfenidone in accordance with the dose escalation method taught by the present invention.

[0056] In one embodiment, the starter pack further comprises additional rows for Days 15, 16, 17, 18, 19, 20, and 21. In another embodiment, each of the three compartments corresponding to Days 15, 16, 17, 18, 19, 20, and 21 separately contain three pills of 267-mg pirfenidone. The addition of the rows for Days 15, 16, 17, 18, 19, 20, and 21 is for the purpose of training the patient as to the correct amount of dosage that will be needed after the starter pack is finished and the patient begins taking pills from another source, such as a pill bottle. By providing the starter pack with a third week at the full dosage of pirfenidone, the patient will be better accustomed to taking the 2,403 mg/day dosage from Day 15 and each Day thereafter as required by the pirfenidone therapy method of the present invention.

[0057] In another embodiment, the starter pack comprises a circular form. Figure 13 shows a container (130) comprising a base (138) that holds at least one panel (132) having a plurality of compartments (136) for containing a dosage amount of pirfenidone. The panel (132) is circular in shape with compartments (136) extending in a radial pattern from the center and wherein each radius designates its own Day for treatment with pirfenidone. The dosages for AM, noon, and PM may be separated in a manner shown in Figure 13. The container (130) also comprises a lid (139) so that at least one panel (132) containing pirfenidone can be stored within the container (130) and sealed.

[0058] Figure 14 shows a portion of a starter pack comprising dosage amounts for the first week of therapy using pirfenidone. The starter pack (140) for the first week of

treatment may comprise a circular panel (142) having a plurality of compartments (146) for containing a dosage amount (148) of pirfenidone. The compartments (146) may be arranged so that they extend radially from the center of the pane (142). The panel (142) may comprise indicia informing the patient which dosage to administer at the appropriate time.

[0059] Figure 15 shows a portion of a starter pack comprising dosage amounts for the second week of therapy using pirfenidone. The starter pack (150) for the second week of treatment may comprise a circular panel (152) having a plurality of compartments (156) for containing a dosage amount (158) of pirfenidone. The compartments (156) may be arranged so that they extend radially from the center or so that they fit within a panel. The panel (152) may comprise indicia informing the patient which dosage to administer at the appropriate time.

[0060] Figure 16 shows a portion of a starter pack comprising dosage amounts for the third week of therapy using pirfenidone. The panel for the third week of therapy is optionally provided. The starter pack (160) for the third week of treatment may comprise a circular panel (162) having a plurality of compartments (166) for containing a dosage amount (168) of pirfenidone. The compartments (146) may be arranged so that they extend radially from the center of the pane (162). The panel (162) may comprise indicia informing the patient which dosage to administer at the appropriate time.

[0061] In another embodiment, the starter pack has compartments arranged such that a user of the starter pack will administer the pirfenidone in accordance with the dose escalation method taught by the present invention. Of course, as an alternative to blister packs, the doses can be contained in any other type of compartment, such as plastic bags or other containers fastened together in book form; plastic containers with snap-open lids arranged in a row or other geometric pattern, or any of a wide variety of other dosage containing packages.

Claims

1. Pirfenidone, in an initial dose escalation regimen, for use in treating idiopathic pulmonary fibrosis (IPF), wherein the pirfenidone is for:

   administering to a patient a first oral daily dosage of 801 mg as one capsule comprising 267-mg of pirfenidone three times a day for days one to seven of the dose escalation regimen;
   administering to the patient a second oral daily dosage of 1602 mg as two capsules comprising 267-mg of pirfenidone three times a day for days eight to fourteen of the dose escalation regimen; and
   administering to the patient a third oral daily dosage of 2403 mg as three capsules comprising 267-mg of pirfenidone three times a day for at least day fifteen of the dose escalation regimen; and
   wherein said dosages are for taking with food.

2. Use of pirfenidone in the manufacture of a medicament for treating idiopathic pulmonary fibrosis (IPF), wherein the medicament is for:

   administering to a patient a first oral dally dosage of 801 mg as one capsule comprising 267-mg of pirfenidone three times a day for days one to seven of a dose escalation regimen;
   administering to the patient a second oral daily dosage of 1602 mg as two capsules comprising 267-mg of pirfenidone three times a day for days eight to fourteen of the dose escalation regimen; and
   administering to the patient a third oral daily dosage of 2403 mg as three capsules comprising 267-mg of pirfenidone three times a day for at least day fifteen of the dose escalation regimen; and
   wherein said dosages are for taking with food.

3. A starter pack comprising:

   a first set of compartments each having a first dosage amount of pirfenidone that is 801 mg per day as one pill comprising 267-mg of pirfenidone three times a day; and
   a second set of compartments each having a second dosage amount of pirfenidone that is 1602 mg per day as two pills comprising 267-mg of pirfenidone three times a day; and
   at least one additional set of compartments each having a third dosage amount of pirfenidone that is 2403 mg as three pills comprising 267-mg of pirfenidone three times a day,
   wherein the first set of compartments are for administering the first dosage amount of pirfenidone for Days 1, 2, 3, 4, 5, 6 and 7, and wherein the second set of compartments are for administering a second dosage amount of pirfenidone for Days 8, 9, 10, 11, 12, 13 and 14, and wherein the additional set of compartments are for administering a third dosage amount of pirfenidone beginning on Day 15.

4. The pirfenidone or use according to Claim 1 or 2, wherein the initial dose escalation regimen reduces the incidence of an adverse event associated with the administration of pirfenidone.

Patentansprüche

1. Verwendung von Pirfenidon, in einer Verordnung mit anfänglicher Dosissteigerung, zum Behandeln idio-

pathischer Lungenfibrose (IPF), bei der das Pirfenidon dient:

zum Verabreichen einer ersten täglichen oralen Dosierung von 801 mg an einen Patienten als eine 267-mg Pirfenidon enthaltende Kapsel, dreimal täglich an den Tagen eins bis sieben der Verordnung mit anfänglicher Dosissteigerung;
zum Verabreichen einer zweiten täglichen oralen Dosierung von 1602 mg an einen Patienten als eine 267-mg Pirfenidon enthaltende Kapsel, dreimal täglich an den Tagen acht bis vierzehn der Verordnung mit anfänglicher Dosissteigerung; und
zum Verabreichen einer dritten täglichen oralen Dosierung von 2403 mg an einen Patienten als eine 267-mg Pirfenidon enthaltende Kapsel, dreimal täglich mindestens am Tag fünfzehn der Verordnung mit anfänglicher Dosissteigerung; und

worin genannte Dosierungen mit Nahrung einzunehmen sind.

2. Verwendung von Pirfenidon bei der Herstellung eines Medikamentes zum Behandeln idiopathischer Lungenfibrose (IPF), worin das Medikament dient:

zum Verabreichen einer ersten täglichen oralen Dosierung von 801 mg an einen Patienten als eine 267-mg Pirfenidon enthaltende Kapsel, dreimal täglich an den Tagen eins bis sieben der Verordnung mit anfänglicher Dosissteigerung;
zum Verabreichen einer zweiten täglichen oralen Dosierung von 1602 mg an einen Patienten als eine 267-mg Pirfenidon enthaltende Kapsel, dreimal täglich an den Tagen acht bis vierzehn der Verordnung mit anfänglicher Dosissteigerung; und
zum Verabreichen einer dritten täglichen oralen Dosierung von 2403 mg an einen Patienten als eine 267-mg Pirfenidon enthaltende Kapsel, dreimal täglich mindestens am Tag fünfzehn der Verordnung mit anfänglicher Dosissteigerung; und

worin genannte Dosierungen mit Nahrung einzunehmen sind.

3. Starterpaket umfassend:

einen ersten Satz an Fächern, jedes mit einer ersten Dosierungsmenge von Pirfenidon, die 801 mg pro Tag beträgt als eine 267-mg Pirfenidon enthaltende Pille, dreimal täglich; und
einen zweiten Satz an Fächern, jedes mit einer zweiten Dosierungsmenge von Pirfenidon, die 1602 mg pro Tag beträgt als zwei 267-mg an Pirfenidon enthaltende Pillen, dreimal täglich; und
mindestens ein zusätzlicher Satz an Fächern, jedes mit einer dritten Dosierungsmenge von Pirfenidon, die 2403 mg beträgt als drei 267-mg an Pirfenidon enthaltende Pillen, dreimal täglich,
worin der erste Satz an Fächern zum Verabreichen der ersten Dosierungsmenge von Pirfenidon für die Tage 1, 2, 3, 4, 5, 6 und 7 dient, und worin der zweite Satz an Fächern zum Verabreichen einer zweiten Dosierungsmenge von Pirfenidon für die Tage 8, 9, 10, 11, 12, 13 und 14 dient, und worin der zusätzliche Satz an Fächern zum Verabreichen einer dritten Dosierungsmenge von Pirfenidon beginnend mit Tag 15 dient.

4. Pirfenidon oder Verwendung nach Anspruch 1 oder 2, worin die erste Verordnung mit anfänglicher Dosissteigerung das Auftreten eines negativen Ereignisses im Zusammenhang mit der Verabreichung von Pirfenidon reduziert.

Revendications

1. Pirfénidone, dans un schéma posologique initial à doses croissantes, pour l'utilisation dans le traitement de la fibrose pulmonaire idiopathique (FPI), où la pirfénidone est destinée à
être administrée à un patient à une première dose quotidienne orale de 801 mg sous forme d'une gélule comprenant 267 mg de pirfénidone trois fois par jour pendant les jours un à sept du schéma posologique à doses croissantes ;
être administrée au patient à une deuxième dose quotidienne orale de 1 602 mg sous forme de deux gélules comprenant 267 mg de pirfénidone trois fois par jour pendant les jours huit à quatorze du schéma posologique à doses croissantes ; et
être administrée au patient à une troisième dose quotidienne orale de 2 403 mg sous forme de trois gélules comprenant 267 mg de pirfénidone trois fois par jour pendant au moins le jour quinze du schéma posologique à doses croissantes ; et
où lesdites doses sont à prendre avec un aliment.

2. Utilisation de pirfénidone dans la fabrication d'un médicament destiné à traiter la fibrose pulmonaire idiopathique (FPI), dans laquelle le médicament est destiné à :

être administré à un patient à une première dose quotidienne orale de 801 mg sous forme d'une gélule comprenant 267 mg de pirfénidone trois fois par jour pendant les jours un à sept d'un schéma posologique à doses croissantes ;

être administré au patient à une deuxième dose quotidienne orale de 1 602 mg sous forme de deux gélules comprenant 267 mg de pirfénidone trois fois par jour pendant les jours huit à quatorze du schéma posologique à doses croissantes ; et
être administré à un patient à une troisième dose quotidienne orale de 2 403 mg sous forme de trois gélules comprenant 267 mg de pirfénidone trois fois par jour pendant au moins le jour quinze du schéma posologique à doses croissantes ; et dans laquelle lesdites doses sont à prendre avec un aliment.

3. Kit d'induction comprenant :

un premier jeu de compartiments comportant chacun une première dose de pirfénidone qui est de 801 mg par jour sous forme d'une pilule comprenant 267 mg de pirfénidone trois fois par jour ; et
un deuxième jeu de compartiments comportant chacun une deuxième dose de pirfénidone qui est de 1 602 mg par jour sous forme de deux pilules comprenant 267 mg de pirfénidone trois fois par jour ; et
au moins un jeu additionnel de compartiments comportant chacun une troisième dose de pirfénidone qui est de 2 403 mg par jour sous forme de trois pilules comprenant 267 mg de pirfénidone trois fois par jour ;
dans lequel le premier jeu de compartiments est destiné à administrer la première dose de pirfénidone les jours 1, 2, 3, 4, 5, 6 et 7, et dans lequel le deuxième jeu de compartiments est destiné à administrer une deuxième dose de pirfénidone les jours 8, 9, 10, 11, 12, 13 et 14, et dans lequel le jeu additionnel de compartiments est destiné à administrer une troisième dose de pirfénidone commençant le jour 15.

4. Pirfénidone ou utilisation selon la revendication 1 ou 2, où le schéma posologique initial à doses croissantes réduit l'incidence d'un effet indésirable associé à l'administration de pirfénidone.

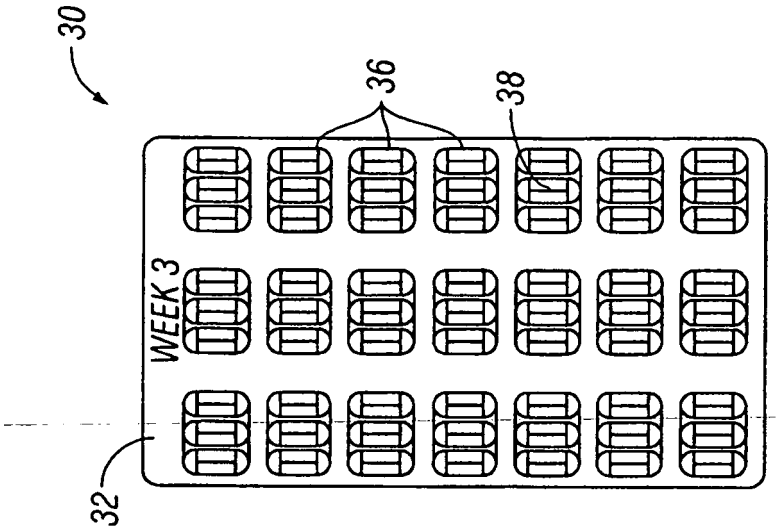

FIG. 3

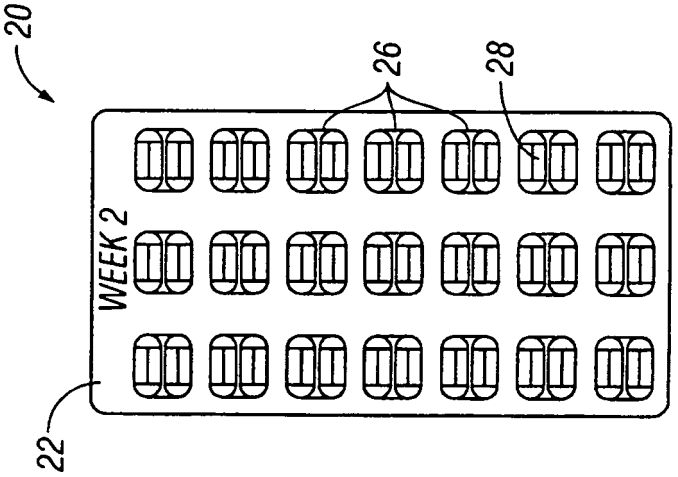

FIG. 2

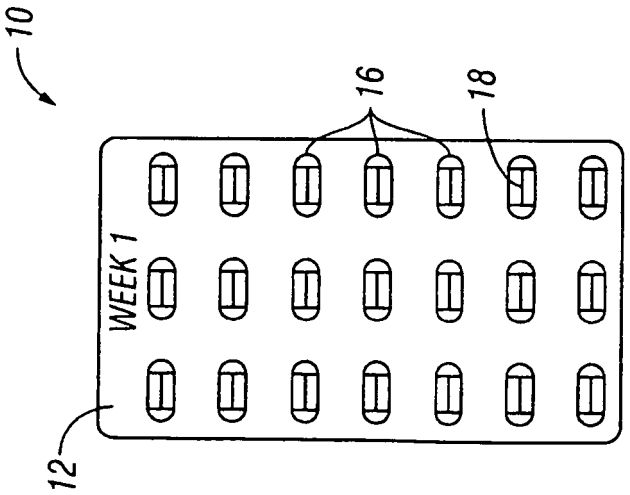

FIG. 1

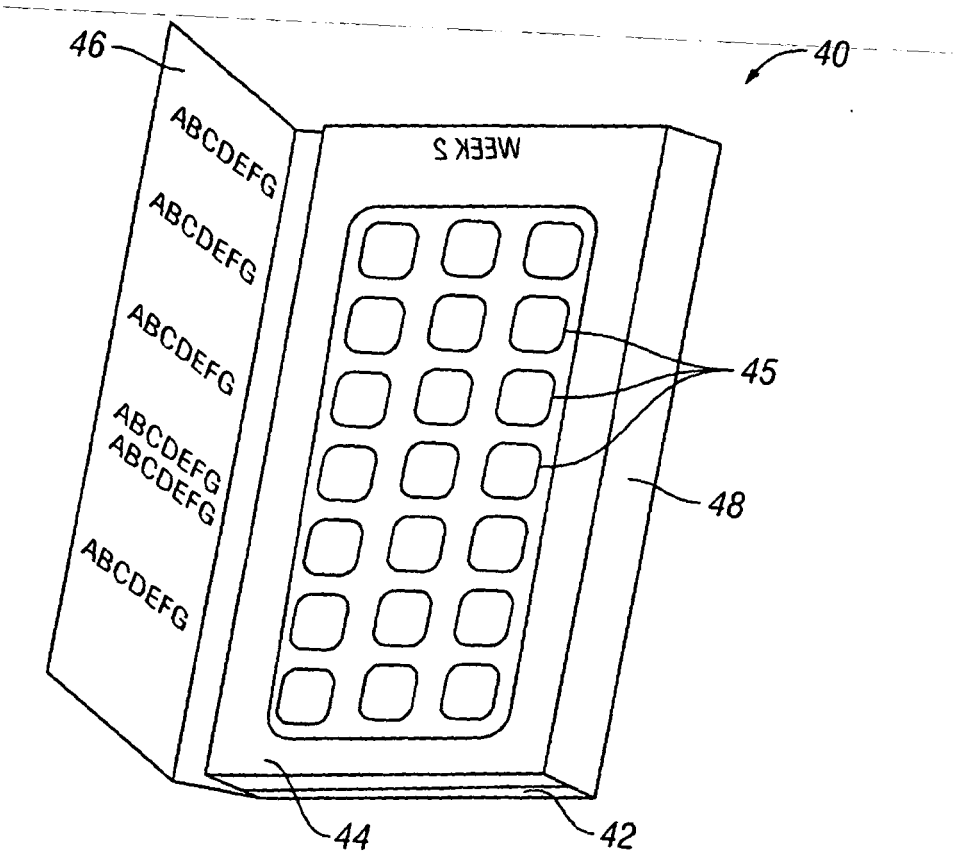
46
40
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
WEEK 5
45
48
44
42

FIG. 4

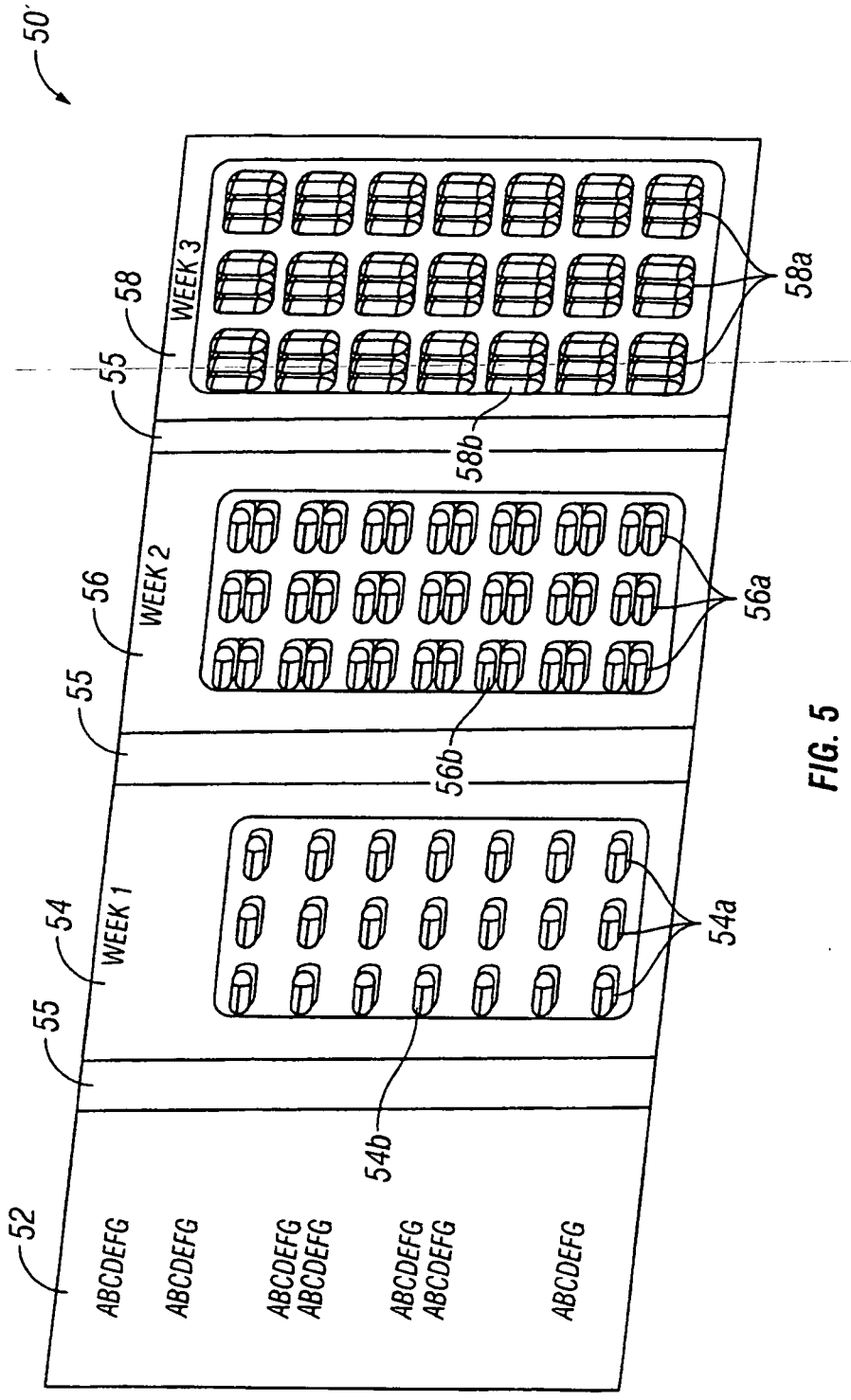
50'
58
WEEK 3
58a
55
58b
56
WEEK 2
56a
55
56b
54
WEEK 1
54a
55
54b
52
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG

FIG. 5

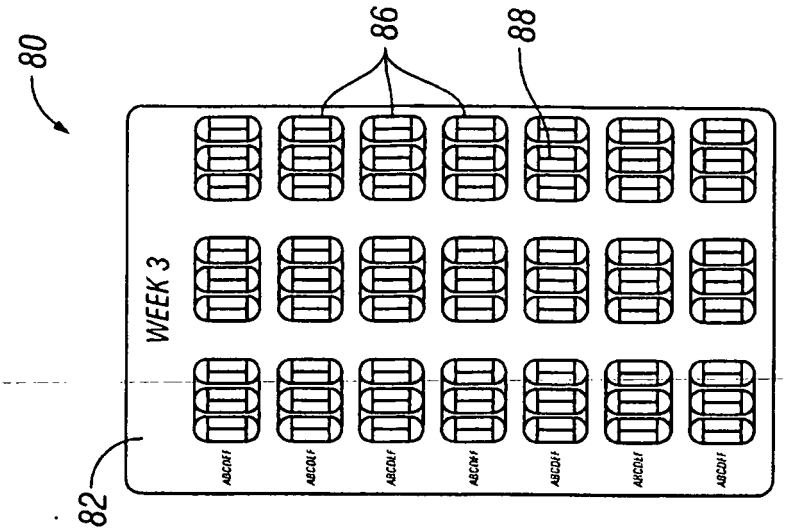

FIG. 8

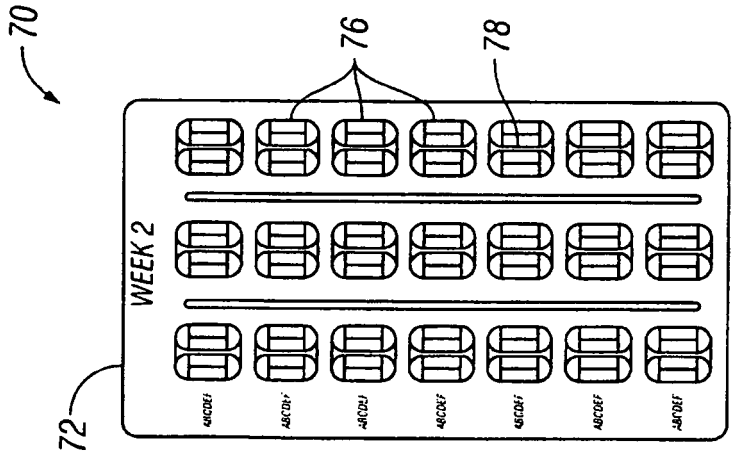

FIG. 7

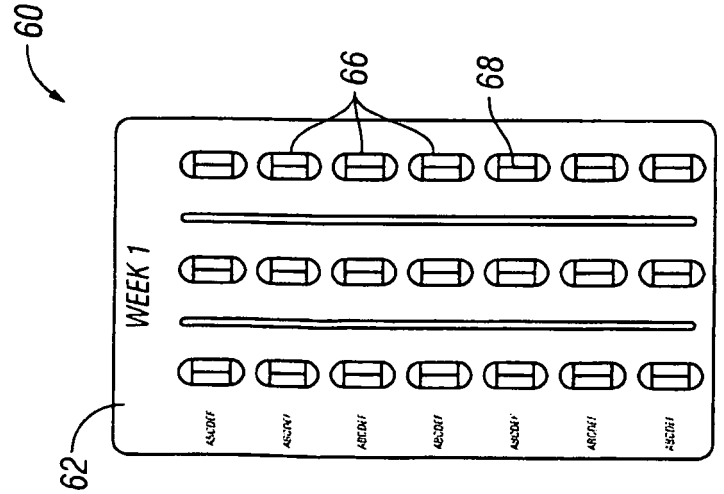

FIG. 6

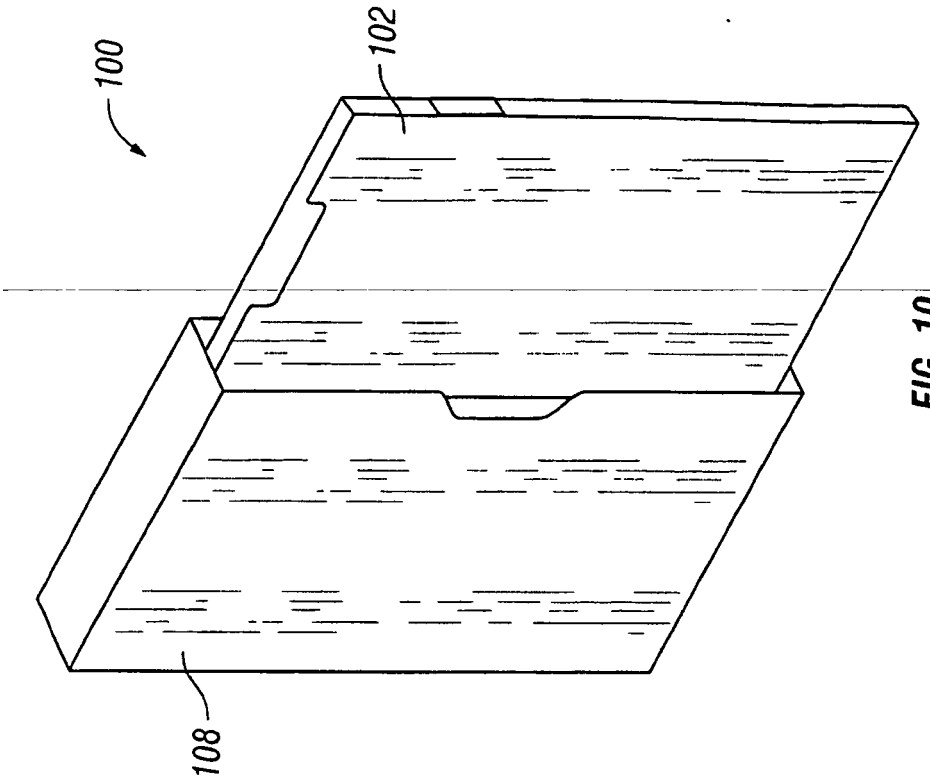

FIG. 10

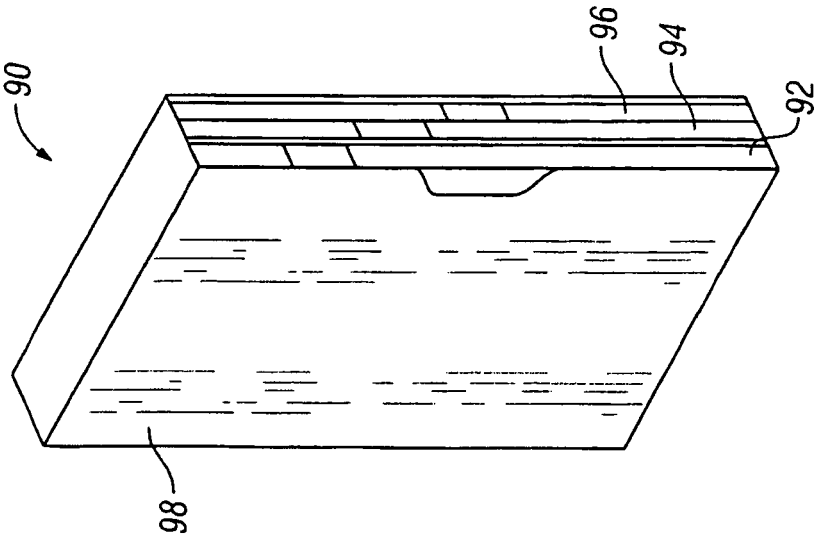

FIG. 9

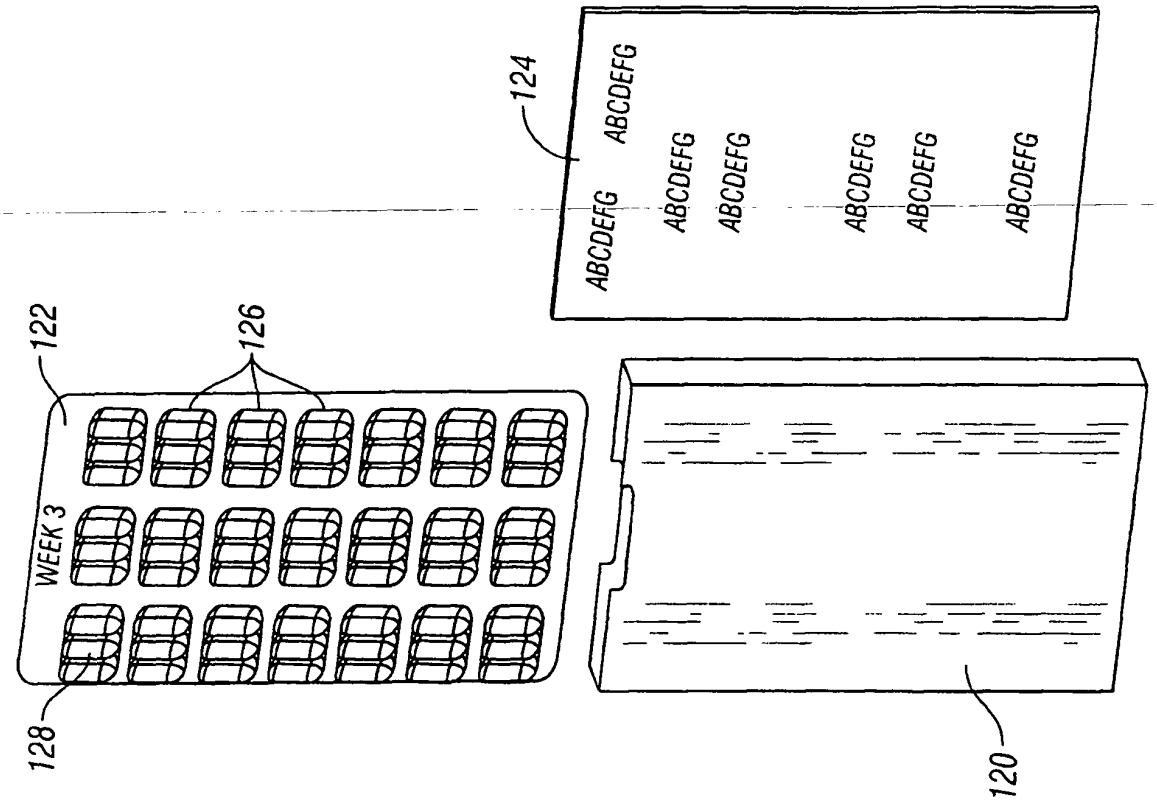
124
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
122
126
WEEK 3
128
120

FIG. 12

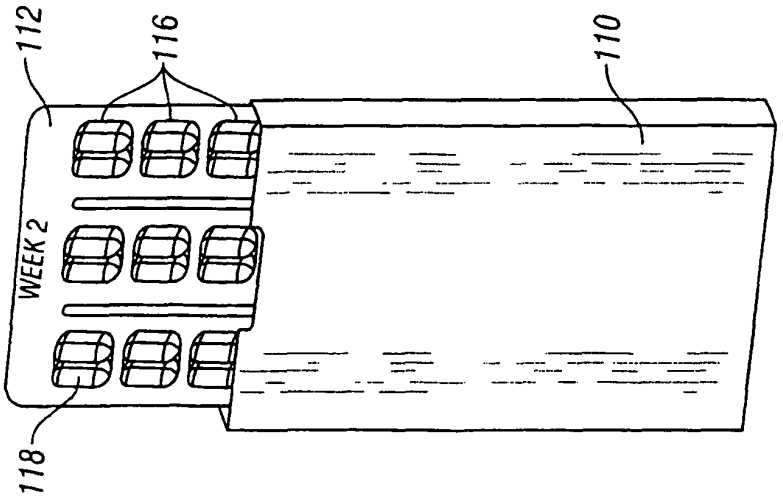
112
116
110
WEEK 2
118

FIG. 11

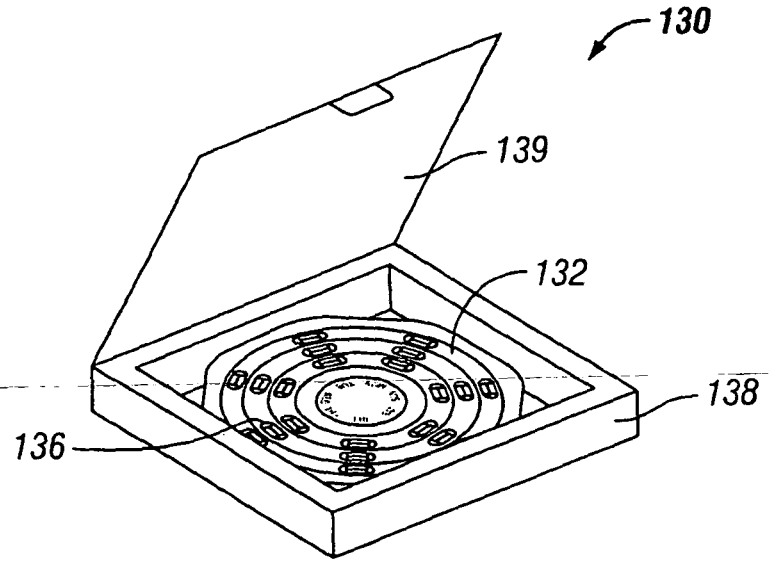

FIG. 13

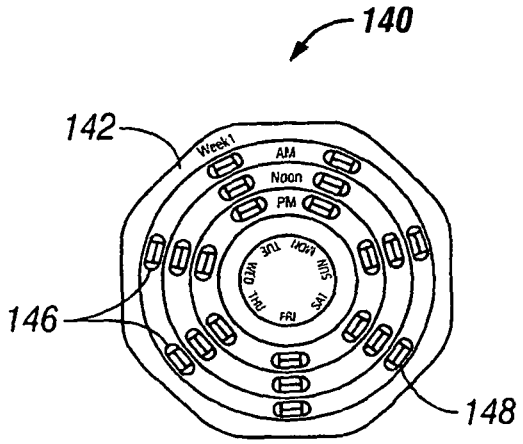

FIG. 14

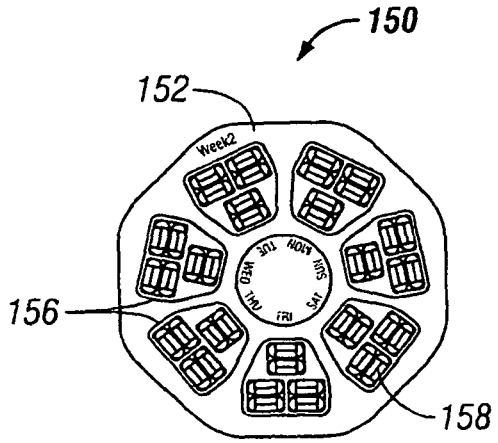

FIG. 15

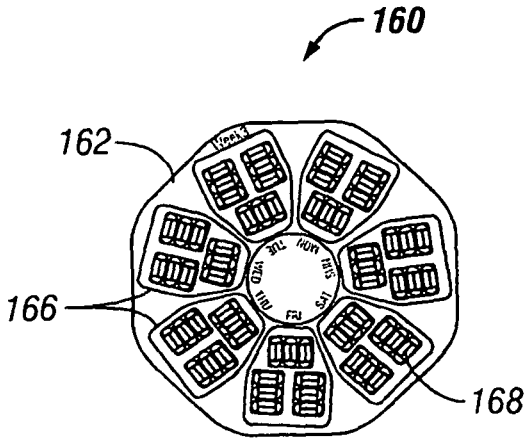

FIG. 16

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- **Zhang S et al.** *Australian and New England J Ophthalmology,* 1998, vol. 26, S74-S76 **[0004]**
- **Cain et al.** *Int'l J Immunopharmacology,* 1998, vol. 20, 685-695 **[0004]**
- **Azuma, A. et al.** *Am J Respir Crit Care Med,* 2005, vol. 171, 1040-47 **[0006]**