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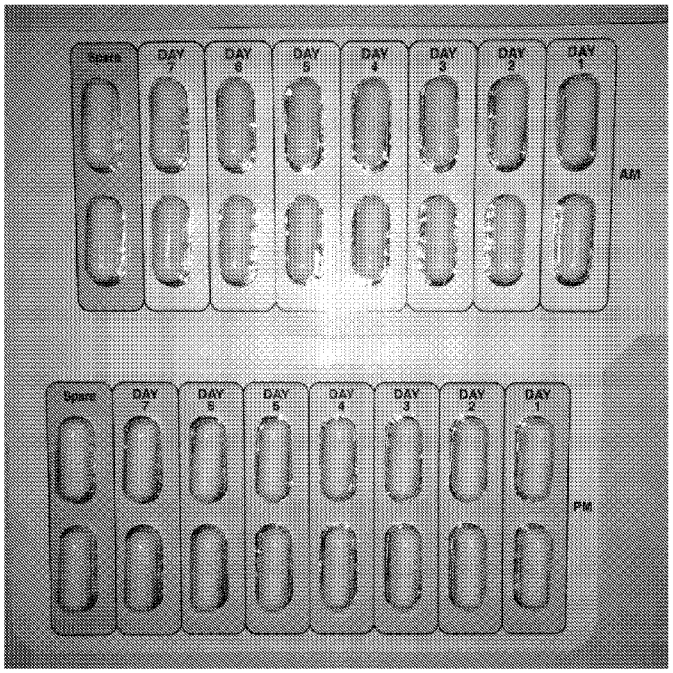
(54) Title: COMBINATION DRUG THERAPIES FOR CANCER AND METHODS OF MAKING AND USING THEM

FIG. 2



(57) Abstract: In alternative embodiments, provided are therapeutic combinations, pharmaceutical compositions, formulations, kits and devices for treating, preventing or ameliorating a tumor or a cancer, and methods for treating, preventing or ameliorating a tumor or a cancer. In alternative embodiments, provided are therapeutic combinations, pharmaceutical compositions, formulations, kits and devices comprising: a beta adrenergic receptor antagonist (a "beta blocker", such as propranolol); a non-steroidal anti-inflammatory drug (a NSAID, such as etodolac) packaged or formulated for chronodosed and pulsatile release such that they can be administered two times a day (BID), and methods for making and using them, e.g., in treatment regimens. In alternative embodiments, the therapeutic combinations of therapeutic agents or drugs further comprise an anti-cancer or anti-tumor antibody, a cytokine, and/or another chemotherapeutic agent.

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COMBINATION DRUG THERAPIES FOR CANCER AND METHODS OF MAKING AND USING THEM

RELATED APPLICATIONS

This Patent Convention Treaty (PCT) international application claims the benefit of priority to U.S. Provisional Patent Applications Serial Nos. (USSN) 62/580,969, filed November 02, 2017; USSN 62/582,136, filed November 06, 2017; and USSN 62/630,066, filed February 13, 2018. The aforementioned applications are expressly incorporated herein by reference in their entirety and for all purposes.

FIELD OF THE INVENTION

This invention relates generally to medicine, pharmaceutical formulations and medical devices. In alternative embodiments, provided are therapeutic combinations, pharmaceutical compositions, formulations, kits and devices for treating, preventing or ameliorating a tumor or a cancer, and methods for treating, preventing or ameliorating a tumor or a cancer. In alternative embodiments, provided are therapeutic combinations, pharmaceutical compositions, formulations, kits and devices comprising: a beta-adrenergic receptor antagonist (a "beta blocker", such as propranolol); and, a non-steroidal anti-inflammatory drug (a NSAID, such as etodolac), packaged or formulated for chronodosed and pulsatile release such that they can be administered two times a day (BID), and methods for making and using them, e.g., in treatment regimens. In alternative embodiments, the therapeutic combinations of therapeutic agents or drugs comprise an anti-cancer or anti-tumor antibody, a cytokine, and/or another chemotherapeutic agent.

BACKGROUND

Chemotherapy is important in cancer treatment, but chemotherapy drugs act by damaging high proliferating cells, and damage to normal cells results in chemotherapy toxicities and side effects. Chemotoxicity can be seen most in actively dividing tissues such bone marrow, hair follicles and gastrointestinal mucosa and in non-dividing, but toxicity sensitive, nerves. New approaches in cancer chemotherapeutics are needed to address these challenges.

Barillet 2015 British J of Clinical Pharm vol 80:6, pgs 1289-1302, established that adherence by patients to time-interval administration (80% of the time, within two hours) of orally administered anti-cancer drugs is only between about 25% to 50%, and this amount goes down when more than one drug is administered, patients are elderly or have many symptoms, have no spouse or other risk factors of poor adherence. The overall rates of patient adherence to long term oral therapy reach no more than 50% in developed countries. The increased number of prescribed medications for multiple comorbid conditions may further compromise adherence to treatment due to the confusion between treatment regimens. Moreover, age-related issues, such as visual and cognitive impairment, memory deficits, functional decline, unpleasant side effects, and lack of social support may have a negative impact on adherence to oral treatment regimens. In a variety of patient populations, nonadherence and non-persistence have been associated with treatment failure and associated increased consumption of healthcare resources, including an increased number of physician visits, higher hospitalization rates and longer stays. There is a clear need for more effective and reliable systems and safeguards that ensure patient compliance with orally, self-administered anti-cancer therapies.

While the combination of coxibs (nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase-2 (COX-2) but not cyclooxygenase-1 (COX-1)) such as etodolac in combination with beta adrenergic receptor antagonists ("beta blockers") such as propranolol have been shown to have activity for the treatment of cancer, as yet unsolved problems present themselves using this therapeutic combination, for example: daily neuro-immuno oscillations and side effects limit the ability to co-administer beta blockers and coxibs twice-a-day (BID) in the AM and PM; it is difficult for medical practitioners to titrate varying drug amounts of combinations of individual pills needed to determine a tolerable yet efficacious dose, and this limits their use, safety and efficacy; and, it is difficult to get patients to comply or adhere to a three times a day (TID) dosing regimen using varying drug amounts of combinations of pills – because all these problems are yet unsolved the currently used treatment regimen for coxibs and beta blockers is a three times a day (TID) dosing regimen. Current dosage regimens combining coxibs and beta blockers can show significant efficacy and safety for advanced cancers, but they are formulated and dosaged for at least TID, at different dose ratios, and – in addition to the problems listed above - have complex titration requirements, all of which are impractical in a community, versus a clinical trials, setting. New formulations

and dosaging regimens for coxib-beta blocker co-administration are needed to address these problems.

SUMMARY

In alternative embodiments, provided are pharmaceutical dosage forms, drug delivery devices or products of manufacture, comprising:

(a) a first formulation comprising or consisting of:

(i) a delayed (or controlled) release (DR) propranolol formulation and an immediate release (IR) propranolol formulation; and,

(ii) an immediate release (IR) etodolac formulation; and

(b) a second formulation comprising or consisting of an immediate release (IR) etodolac formulation,

wherein optionally the first formulation is formulated or manufactured as having the delayed (or controlled) release (DR) propranolol formulation, and/or the immediate release (IR) propranolol formulation, on or coated on the surface of or contained: in a bead, a powder, a particle, or a multilayered bead or particle,

wherein optionally the second formulation is formulated or manufactured as having the immediate release (IR) etodolac formulation, on or coated on the surface of or contained in: a bead, a powder, a particle, or a multilayered bead or particle,

and optionally the bead, powder, particle or the multilayered bead or particle is contained in a pill, a capsule, a tablet, or a geltab, or equivalents, for oral delivery,

wherein optionally the pill, capsule, tablet, geltab or equivalent for oral delivery is a hard gelatin capsule or equivalent, or comprises a hard gelatin or equivalent,

wherein:

the delayed (or controlled) release (DR) propranolol formulation comprises a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof,

the immediate release (IR) propranolol formulation comprises a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof, and

the immediate release (IR) etodolac formulation comprises a racemic R(+) and S(–) mixture of etodolac, a substantially pure (S)-enantiomer of etodolac, or a pharmaceutically acceptable salt thereof, or mixtures thereof,

and optionally the immediate release (IR) propranolol formulation comprises particles, powders, pellets, or beads (or a core comprising particles, powders, pellets, or beads), and the particles, powders, pellets, or beads are coated with or have contained therein:

a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof;

and optionally the immediate release (IR) etodolac formulation comprises particles, powders, pellets, or beads (or a core comprising particles, powders, pellets, or beads), and the particles, powders, pellets, or beads are coated with or have contained therein:

a racemic R(+) and S(–) mixture of etodolac, a substantially pure (S)-enantiomer of etodolac, or a pharmaceutically acceptable salt thereof, or mixtures thereof;

and optionally the delayed (or controlled) release (DR) propranolol formulation comprises particles, pellets, or beads (or a core comprising particles, pellets, or beads), and the particles, pellets, or beads are coated with or have contained therein:

a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof, and,

the optionally particles, powders, pellets, or beads comprise a membrane or a coating comprising a water insoluble polymer or a combination of a water insoluble polymer and a water soluble polymer,

wherein the pharmaceutical dosage form, the drug delivery device or the product of manufacture exhibits the following *in vitro* dissolution profile, or *in vivo* human dissolution profile,

wherein optionally the *in vitro* dissolution profile is determined by testing according to United States Pharmacopoeia dissolution test method USP Apparatus 1, Baskets @ 100 rpm, Drug Release Test 1 using 900 mL of pH 1.2 buffer for 1.5 hours followed by testing in 900 mL of pH 6.8 at 4, 8, 14, and 24 hours,

and the *in vivo* human dissolution profile is based on an oral administration to an individual in need thereof:

after 1.0 hour: not less than about 35%, 40%, 45% or 50% of the total propranolol is released (or dissolved); or, about 50% +/- 15%, of the total propranolol is released (or dissolved);

after 2 hours: about 55 +/- 15% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 4 hours: about 60 +/- 15% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 6 hours: about 80 +/- 15% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test; and,

after 8 hours: not less than about 90% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test.

In alternative embodiments, the dissolution profile corresponds to the following pattern:

(a) after 1.0 hour: not less than about 50% +/- 10%, of the total propranolol is released (or dissolved);

after 2 hours: about 55 +/- 10% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 3 hours: about 60 +/- 10% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 6 hours: about 80 +/- 10% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test; and,

after 8 hours: not less than about 95% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

or

(b) after 1.0 hour: about 50% +/- 5%, of the total propranolol is released (or dissolved);

after 2 hours: about 55 +/- 5% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 3 hours: about 60 +/- 5% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 6 hours: about 80 +/- 5% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test; and,

after 8 hours: not less than about 97% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test.

In alternative embodiments, the first formulation, the amount of propranolol in the delayed (or controlled) release (DR) propranolol formulation and the amount of propranolol in the immediate release (IR) propranolol formulation are present in a ratio of from:

about 99:1 to 80:20 or 60:40 or 40:60,

about 95:5 to 75:25 or 65:35 or 55:45 or 45:55 or 35:65, or

about 10:90 to 30:70 or 50:50 or 70:30.

In alternative embodiments, the first formulation the immediate release (IR) propranolol formulation substantially releases all of the racemic R(+) and S(–) mixture of propranolol, the substantially pure (S)-enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, contained therein during the first hour of dissolution testing, or during the first hour after oral administration.

In alternative embodiments, the first formulation and/or the second formulation the immediate release (IR) etodolac formulation substantially releases all of the racemic R(+) and S(–) mixture of etodolac, the substantially pure (S)-enantiomer of etodolac, or the pharmaceutically acceptable salt thereof, or mixtures thereof, contained therein during the first hour of dissolution testing, or during the first hour after oral administration.

In alternative embodiments, the water insoluble polymer comprises an ethylcellulose, a cellulose acetate, an ammonio methacrylic acid copolymer, or mixtures thereof. In alternative embodiments, the water-insoluble polymer and water-soluble polymer are present in a weight ratio of from about 0:100 to 60:40.

In alternative embodiments, the core particles or beads comprise or are manufactured as sugar spheres, cellulose spheres, silicone dioxide spheroids, acidic buffer crystals, or alkaline buffer crystals. In alternative embodiments, the core particles or beads further comprise: (a) a polymeric binder; (b) a seal coating; or, (c) non-pareil seeds and a polymeric binder in the immediate release (IR) propranolol formulation or the immediate release (IR) etodolac formulation.

In alternative embodiments, the water-soluble polymer comprises a hydroxypropylcellulose, a hydroxypropylmethylcellulose, a methylcellulose, a polyethylene glycol, a polyvinylpyrrolidone or a mixture thereof.

In alternative embodiments, the pharmaceutical dosage form, the drug delivery device or the product of manufacture is configured or manufactured as a blister card or equivalent, wherein at least one day, or between about one to two weeks, or 7 to 8 days, of:

(a) the first formulation for administration in the morning or breakfast (or AM, or afternoon) are formulated in a single orally administrable carrier, or 2 or 3 orally administrable carriers (optionally one, two or three or more tablets, capsules, geltabs, or pills or equivalents), and,

(b) the second formulation for administration at dinnertime or the evening (or in the PM or at bedtime) comprising an immediate release (IR) etodolac, formulated in a single orally administrable carrier, or 2 or 3 orally administrable carriers (optionally one, two or three or more tablets, capsules, geltabs, or pills or equivalents),

are packaged in the blister card or equivalent in separate compartments (wherein the one, two or three or more orally administrable carriers of (a) and the one, two or three or more orally administrable carriers (b) are in separate compartments on the blister card),

and optionally, between about two days and one to two weeks, or about 8 days, of the one, two or three or more orally administrable carriers of the first formulation, and separately the one, two or three or more orally administrable carriers of the second formulation, are packaged and configured or spaced on the blister card or equivalent in relation to each other to reflect an administration regimen wherein the one, two or three or more orally administrable carriers of the first formulation is to be taken in the AM (morning or afternoon) and the one, two or three or more orally administrable carriers of the second formulation are to be taken in at dinnertime or the evening (or in the PM or at bedtime),

wherein optionally the blister card or equivalent comprises at least a first and a second blister strip, wherein the first blister strip contains or comprises between about two days and one to two weeks, or about 7 or 8 days, of the one, two or three or more orally administrable carriers of the first formulation to be taken in the AM (morning or afternoon); and the second blister strip contains or comprises between about two days and one to two weeks, or about 7 to 8 days, of the one, two or three or more orally administrable carriers of the second formulation to be taken at dinnertime or in the evening (or in the PM or at bedtime),

and optionally the one, two or three or more orally administrable carriers of the second formulation comprise immediate release (IR) etodolac formulation contained in or on or coated on a plurality of particles, a powder, pellets, or beads (or contained in or on or coated on a core comprising particles, a powder, pellets, or beads), and the IR etodolac formulation comprises:

a racemic R(+) and S(–) mixture of etodolac, a substantially pure (S)-enantiomer of etodolac, or a pharmaceutically acceptable salt thereof, or mixtures thereof;

and optionally the one, two or three or more orally administrable carriers of the second formulation are arranged in a blister card or equivalent for administration at dinnertime or in the evening or at bedtime (or in the PM) and that each administrable carrier has or all the administrable carriers in total have: between about 100 and 500 mg, between about 200 and 400 mg, between about 250 and 350 mg, about 270, or about 200, 210, 220, 225, 230, 240, 250, 260, 270, 275, 280, 290, 300, 310, 320, 330, 340, 350 mg, IR etodolac, or up to three times these amounts, or between about 300 mg and 1,050 mg immediate release (IR) etodolac,

and optionally the blister card or equivalent is a thermoformed polyvinyl chloride (PVC) blister card or equivalent with a push-through lidding (optionally a foil-lined paper push-through lidding, or any air-impermeable lidding), optionally comprising a sealing layer and a moisture barrier, wherein optionally the sealing layer comprises APPEEL®, and optionally the moisture barrier comprises ACLAR®.

In alternative embodiment, the pharmaceutical dosage form, the drug delivery device or the product of manufacture comprises a therapeutic combination comprising:

(a)

- one, two or three or more tablets, pills, geltabs, capsules or equivalents for administration in the morning or in the AM, that each tablet, pill, geltab, capsule or equivalent has, or all tablets, pills, geltabs, capsules or equivalent in a compartment in total have:

about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of immediate release (IR) propranolol, or up to triple these amounts, or between about 12 and 60 mg DR propranolol;

about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of delayed (or controlled) release (DR) propranolol, or up to triple these amounts, or between about 12 and 60 mg DR propranolol; and

about 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130 or 140 mg IR etodolac, or up to triple these amounts, or between about 150 and 420 IR etodolac,

and optionally each of the morning or afternoon, or AM one, two or three or more tablets, pills, geltabs, capsules or equivalents has approximately equal amounts of IR and DR propranolol (optionally about 16 mg IR and about 16 mg DR propranolol for a racemic mixture, totaling 32 mg propranolol in each tablet, or 32 mg total for all the tablets for a particular dose (e.g., all in one blister card container), or about 4 to 12 mg or 6 to 10 mg IR and about 4 to 12 mg or 6 to 10 mg DR propranolol in each tablet, or these totals for all the tablets for a particular dose (e.g., all in one blister card container), for a substantially pure (S)-enantiomer, of propranolol),

and optionally each set of morning or AM one, two or three or more tablets, pills, geltabs, capsules or equivalents are in one blister card or equivalent compartment and the compartments are arranged in the blister card or equivalent for morning or afternoon, or AM consumption, administration or use by a user (or a patient),

wherein optionally if two morning or AM tablets, pills, geltabs, capsules or equivalents have each 32 mg propranolol in each tablet, then the two tablets in the AM compartment total a 64 mg etodolac dosage administration for the AM, and if three morning or AM tablets, pills, geltabs, capsules or equivalents have each 32 mg propranolol in each tablet, then the three tablets in the AM compartment total a 96 mg etodolac dosage administration for the AM; and

the one, two or three or more tablets, pills, geltabs, capsules or equivalents for administration in at dinnertime or in the evening (or in the PM or at bedtime) each having or in total having between about 100 and 500 mg, between about 200 and 400 mg, between about 250 and 350 mg, about 270 mg, or about 200, 210, 220, 225, 230, 240, 250, 260, 270, 275, 280, 290, 300, 310, 320, 330, 340 or 350 mg, IR etodolac, or up to triple these amounts, or between about 300 mg and 1,050 mg IR etodolac,

and optionally each set of at dinnertime or in the evening (or in the PM or at bedtime) one, two or three or more tablets, pills, geltabs, capsules or equivalents are in one blister card or equivalent compartment and the compartments are arranged in the blister card or equivalent for at dinnertime or in the evening (or in the PM or at bedtime) consumption, administration or use by a user (or a patient),

wherein optionally if the two at dinnertime or in the evening (or in the PM or at bedtime) tablets, pills, geltabs, capsules or equivalents each have 270 mg etodolac in each tablet, then the two tablets in the PM compartment total a 540 mg etodolac dosage administration for the PM, and if there are three at dinnertime or in the evening (or in the PM or at bedtime) tablets, pills, geltabs, capsules or equivalents each having 270 mg etodolac in each tablet, then the three tablets in the PM compartment total a 810 mg etodolac dosage administration for the PM; or (b)

- one, two or three or more tablets, pills, geltabs, capsules or equivalents for administration in the morning or breakfast, or AM, that each tablet, pill, geltab, capsule or equivalent has, or all tablets, pills, geltabs, capsules or equivalent in a compartment in total have:

(i) between about 2 to 80 mg, 4 to 40 mg, 5 to 25 mg, or 10 to 20 mg IR propranolol, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of IR propranolol, or up to triple these amounts, or between about 6 and 240 mg; and

between about 2 to 80 mg, 4 to 40 mg, 5 to 25 mg, or 10 to 20 mg IR propranolol, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of DR propranolol, or up to triple these amounts, or between about 6 and 240 mg,

and optionally the morning or breakfast, or AM, tablet has approximately equal amounts of IR and DR propranolol; and

(ii) about between about 200 and 400 mg, between about 250 and 300 mg, about 170 mg, or about 340 mg, IR etodolac, or about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160 or 170 mg IR etodolac, or up to triple these amounts, or between about 180 and 1200 mg IP etodolac,

wherein optionally if there are two of the same tablets, pills, capsules, geltabs or equivalents are in a compartment, then the total dosage administration will be

double the amount of what drug is in each tablet, pill, geltab, capsule or equivalent,

wherein optionally if there are three of the same tablets, pills, capsules, geltabs or equivalents are in a compartment, then the total dosage administration will be triple the amount of what drug is in each tablet, pill, geltab, capsule or equivalent.

In alternative embodiments of the pharmaceutical dosage form, the drug delivery device or the product of manufacture, the membrane or coating: (a) comprises between about 1% to 10% based on the weight of the bead, particle or the multilayered bead or particle; (b) comprises approximately 1.5% to 6% based on the weight of the bead, particle or the multilayered bead or particle in a delayed (or controlled) release (DR) propranolol formulation. In alternative embodiments the water-insoluble polymer comprises an ethylcellulose having a viscosity of not more than 30 cps when tested on a 5% solution at 25°C.

In alternative embodiments, the total amount of:

(a) the delayed (or controlled) release (DR) propranolol formulation and/or the immediate release (IR) propranolol formulation in the first formulation (optionally as one, two or three or more tablets, pills, geltabs, capsules or equivalents) are each or are in total from between about 2 to 80 mg, between about 4 to 40 mg, between about 5 to 25 mg, or between about 10 to 20 mg, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg, or up to triple of each of these amounts, or between about 6 mg to about 240 mg DR propranolol,

and optionally the DR and IR formulations are present in the first formulation in approximately equal amounts; and/or

(b) the immediate release (IR) etodolac formulation in the first formulation is from between about 25 mg to 200 mg, 50 mg to 175 mg, 60 mg to 160 mg, or 70 mg to 150 mg, or about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160 or 170 mg, or up to triple of each of these amounts, or between about 75 mg and 450 mg,

wherein optionally the first formulation comprises:

(i) about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg, or between about 3 and 32 mg, of the delayed (or controlled) release (DR) propranolol formulation, or up to triple of each of these amounts, or between about 6 and 60 mg;

(ii) about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg, or between about 3 and 32 mg, of the immediate release (IR) propranolol formulation, or up to triple of each of these amounts, or between about 6 and 60 mg; and,

(iii) about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160 or 170 mg of the immediate release (IR) etodolac formulation, or up to triple of each of these amounts, or between about 120 and 510 mg,

and optionally all of (i), (ii), and (iii) are separately formulated in one, two or three or more tablets, pills, geltabs, capsules or equivalents,

and optionally the immediate release (IR) propranolol formulation comprises the racemic R(+) and S(–) mixture of propranolol, the substantially pure (S)-enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, coated on microbeads or microparticles or equivalents, optionally polysaccharide microbeads,

and optionally the delayed (or controlled) release (DR) propranolol formulation comprises the racemic R(+) and S(–) mixture of propranolol, the substantially pure (S)-enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, coated on microbeads or microparticles or equivalents, optionally polysaccharide microbeads or microparticles, and further comprising an ammonio methacrylate copolymer dispersion or equivalents (optionally a EUDRAGIT® polymer or equivalents) also coated on the microbeads or microparticles or equivalents,

wherein optionally if two morning or AM tablets, pills, geltabs, capsules or equivalents have each 32 mg propranolol in each tablet, then the two tablets in the AM compartment total a 64 mg etodolac dosage administration for the AM, and if three morning or AM tablets, pills, geltabs, capsules or equivalents have each 32 mg propranolol in each tablet, then the three tablets in the AM compartment total a 96 mg etodolac dosage administration for the AM.

In alternative embodiments, the water-soluble polymer has a viscosity of not more than 200 cps when tested on a 2% aqueous solution at 25°C.

In alternative embodiments the racemic R(+) and S(–) mixture of propranolol, the substantially pure (S)-enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, in the delayed (or controlled) release (DR) propranolol formulation and/or the immediate release (IR) propranolol formulation are contained in or

adsorbed to or onto a core, wherein optionally the core comprises a plurality of sugar spheres, wherein optionally the sugar spheres comprise sugar spheres PF006 or SUGLETS®, and optionally the amount of sugar spheres in the formulation or in each dosage unit is about 21%(w/w), or is between about 20 to 22%(w/w), or is between about 18 to 25%(w/w).

In alternative embodiments, the racemic R(+) and S(–) mixture of propranolol, the substantially pure (S)-enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, in the delayed (or controlled) release (DR) propranolol formulation and/or the immediate release (IR) propranolol formulation is coated with a coating agent,

and optionally with the coating agent the delayed (or controlled) release (DR) propranolol formulation and/or the immediate release (IR) propranolol formulation forms a bead or a pellet,

and optionally the coating agent comprises a water soluble cellulose ether and/or OPADRY®,

and optionally the water soluble cellulose ether comprises a hypromellose, optionally a METHOCEL E5 PREMIUM LV™,

wherein optionally the coating agent comprises both the hypromellose and the OPADRY®, and optionally the hypromellose and the OPADRY® are present in approximately equal amounts in the formulation or each dosage unit;

and optionally the coating agent further comprises about 2.5% (w/w), or between about 2% (w/w) to 3% (w/w), or between about 1% (w/w) to 4% (w/w), of the formulation or each dosage unit.

In alternative embodiments, the coating agent in the delayed (or controlled) release (DR) propranolol formulation further comprises a triethyl citrate, an ammonio methacrylate copolymer dispersion Type A (optionally EUDRAGIT® RL-30D), an ammonio methacrylate copolymer dispersion Type B (optionally EUDRAGIT® RS-30D), or a mixture thereof,

and optionally the coating agent comprises: the hypromellose at between about 1%(w/w) and 1.5%(w/w); the OPADRY® at between about 1%(w/w) and 1.5%(w/w); the ammonio methacrylate copolymer dispersion Type A at between about 0.5%(w/w) to 1.5%(w/w); the ammonio methacrylate copolymer dispersion Type B at between about

8%(w/w) to 9%(w/w) or 7%(w/w) to 10%(w/w); and the triethyl citrate at between about 1%(w/w) to 2%(w/w), of the formulation or each dosage unit,

and optionally the formulation or each dosage unit further comprises a neutral filler, optionally at an amount of between about 5%(w/w) to 6%(w/w), or about 3%(w/w) to 8%(w/w), of the formulation or each dosage unit,

and optionally the neutral filler comprises a talc or a hydrated magnesium silicate.

In alternative embodiments, the racemic R(+) and S(–) mixture of etodolac, the substantially pure (S)-enantiomer of etodolac, or the pharmaceutically acceptable salt thereof, or mixtures thereof, in the immediate release (IR) etodolac formulation comprises a granulated etodolac, or is comprised substantially of granulated etodolac.

In alternative embodiments, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the immediate release (IR) etodolac formulation comprises or is formulated with a filler, a disintegrant a glidant and/or a lubricant,

and optionally: the filler comprises a microcrystalline cellulose (optionally an AVICEL PH101®); the disintegrant comprises a croscarmellose sodium (optionally an Ac-Di-Sol®); the glidant comprises a colloidal silicon dioxide (optionally a Cab-O-Sil® M5P®), and/or the lubricant comprises magnesium stearate or equivalent thereof,

and optionally in the formulation or each dosage unit: the filler is in an amount at between about 4%(w/w) to 5%(w/w) or 3%(w/w) to 6%(w/w); the disintegrant is in an amount at between about 2%(w/w) to 3%(w/w) or 1%(w/w) to 4%(w/w); the glidant is in an amount at between about 0.1%(w/w) to 0.5%(w/w); and/or, the lubricant is in an amount at between about 0.1%(w/w) to 0.5%(w/w).

In alternative embodiments, provided are methods of chronodosing an individual with: a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof; and, a racemic R(+) and S(–) mixture of etodolac, a substantially pure (S)-enantiomer of etodolac, or a pharmaceutically acceptable salt thereof, or mixtures thereof, comprising: administering to the individual a pharmaceutical dosage form, a drug delivery device or a product of manufacture as set forth herein.

In alternative embodiments, provided are methods for treating or ameliorating a cancer, tumor or a dysfunctional cell condition, or a symptom of cancer, tumor or a dysfunctional cell condition, comprising administering or delivering to an individual in

need thereof a pharmaceutical dosage form, a drug delivery device or a product of manufacture as set forth herein,

wherein optionally a lymphocyte-to-monocyte ratio (LMR) of less than 6 or less than 5 or less than 4 or less than 3, is used to select an individual in need thereof; or, a C-reactive protein (CRP)/Albumin ratio of greater than 0.05 or greater than 0.8 or greater than 0.10 or greater than 0.12 or greater than 0.15 or greater 0.18, is used to select an individual in need thereof; or, a neutrophil-to-lymphocyte ratio (NLR) of greater than 2.0 or greater than 3.0 or greater than 4.0 or greater than 5.0, is used to select an individual in need thereof,

wherein optionally the pharmaceutical dosage form, drug delivery device or product of manufacture is administered in conjunction with or as an adjunct therapy with another treatment for cancer,

wherein optionally the pharmaceutical dosage form, drug delivery device or product of manufacture is administered is delivered or administered to the individual in need thereof before, at the same time and/or after the other treatment for cancer.

In alternative embodiments of the methods, the therapeutic combination is administered at a dosage regimen of:

(a)

- one, two or three or more tablets, pills, capsules, geltabs or equivalents for administration in the morning or breakfast, or AM, that each tablet, pill, geltab, capsule or equivalent has, or all tablets, pills, geltabs, capsules or equivalent in a compartment in total have: 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or 32 mg of immediate release (IR) propranolol; 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or 32 mg of delayed (or controlled) release (DR) propranolol; and about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 mg IR etodolac,

and optionally the morning or breakfast, or AM one, two or three or more tablets, pills, capsules, geltabs or equivalents have approximately equal amounts of IR and DR propranolol (optionally about 16 mg IR and 16 mg DR propranolol for a racemic mixture, or 4 to 8 mg IR and 4 to 8 mg DR propranolol for a substantially pure (S)-enantiomer, of propranolol); and

one, two or three or more tablets, pills, capsules, geltabs or equivalents for administration in at dinnertime or the evening (e.g., PM or bedtime) each having or in total having between about 100 and 250 mg, between about 200 and 400 mg, between about 250 and 300 mg, about 270 mg, or about 200, 210, 220, 225, 230, 240, 250, 260, 270, 275, 280, 290, 300, 310, 320, 330, 340 or 350 mg, IR etodolac; or

(b)

- one, two or three or more tablets, pills, capsules, geltabs or equivalents for administration in the morning or breakfast, or AM, that each tablet, pill, geltab, capsule or equivalent has, or all tablets, pills, geltabs, capsules or equivalent in a compartment in total have:

(i) between about 2 to 80 mg, 4 to 40 mg, 5 to 25 mg, or 10 to 20 mg IR propranolol, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of IR propranolol, or up to triple these amounts, or between about 6 and 240 mg; and

between about 2 to 80 mg, 4 to 40 mg, 5 to 25 mg, or 10 to 20 mg IR propranolol, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of DR propranolol, or up to triple these amounts, or between about 6 and 240 mg,

and optionally the morning or breakfast, or AM, tablet has approximately equal amounts of IR and DR propranolol; and

(ii) about between about 200 and 400 mg, between about 250 and 300 mg, about 170 mg, or about 340 mg, IR etodolac, or about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160 or 170 mg IR etodolac, or up to triple these amounts, or between about 180 and 1200 mg IP etodolac,

wherein optionally if there are two of the same tablets, pills, capsules, geltabs or equivalents are in a compartment, then the total dosage administration will be double the amount of what drug is in each tablet, pill, geltab, capsule or equivalent,

wherein optionally if there are three of the same tablets, pills, capsules, geltabs or equivalents are in a compartment, then the total dosage administration will be triple the amount of what drug is in each tablet, pill, geltab, capsule or equivalent.

In alternative embodiments of the methods, or a pharmaceutical dosage form, the drug delivery device or the product of manufacture as set forth herein, the water insoluble

polymer comprises an ethylcellulose having a viscosity of not more than 30 cps when tested on a 5% solution at 25°C.

In alternative embodiments, provided are drug delivery devices or packages, blister packages (or blister packs), clamshells or trays, comprising a pharmaceutical dosage form or formulation of any of the preceding claims, wherein the drug delivery device or package, blister pack, clamshell or tray comprises a plurality of compartments spatially arranged on the drug delivery device or package, blister pack, clamshell or tray to follow a dosage administration regimen,

wherein the spatially arranged plurality of compartments are in at least two rows, each row marked for the time for which the tablets, pills, capsules, geltabs or equivalents are to be taken by a user (optionally a patient), optionally one row marked for morning, breakfast or AM administration, and one row marked for evening, dinnertime or PM administration, and optionally the row or rows marked for morning, breakfast or AM administration is or are positioned above the row or rows marked for evening, dinnertime or PM administration,

and optionally the spatially arranged plurality of compartments are in four rows, two rows marked for morning, breakfast or AM administration, and two rows marked for evening, dinnertime or PM administration,

and optionally each row comprises seven compartments for one dosage administration for each day of the week, or eight compartments for one dosage administration for each day of the week and one spare, and optionally each vertically arranged set of compartments, or columns, are marked for which day of the week the dosage formulations contained therein are to be taken by the user, and optionally where the drug delivery device or package, blister pack, clamshell or tray has one row for morning, breakfast or AM administration, and one row marked for evening, dinnertime or PM administration, each column or day will have two compartments, optionally where the compartment for morning, breakfast or AM administration is above the compartment for evening, dinnertime or PM administration, and optionally the rows of compartments on the drug delivery device or package, blister package, clamshell or tray is arranged as set forth in FIG. 2,

and optionally each compartment has a foil or equivalent backing, or each compartment is an environmentally- (optionally moisture-, pathogen-, and/or light-) protected or sealed storage unit, and optionally the foil backing requires minimal finger

strength to remove a dosage formulation (optionally one, two or three or more capsules, tablets, pills, geltabs or equivalents) in the compartment;

and optionally the blister package is a face seal blister package, a gang run blister package, a mock blister package, an interactive blister package or a slide blister package,

and optionally the drug delivery device or package, blister package, clamshell or tray is joined with board material which allows the product to be packaged, handled, hung, displayed and/or shipped without damaging the blister protection or seal, and optionally also provided with child resistant features,

and optionally the drug delivery device or package, blister package, clamshell or tray comprises a medical electronic monitory system that records administration time and transmits information to near-field communication (NFC) enabled mobile phone.

In alternative embodiment, provided are pharmaceutical dosage forms, drug delivery devices or packages, blister packages, clamshells or trays, or products of manufacture as provided herein, optionally for use in treating or ameliorating a cancer, tumor or a dysfunctional cell condition, or a symptom of cancer, tumor or a dysfunctional cell condition, further comprising an additional drug or active agent,

and optionally the additional drug or active agent comprises a (optionally an additional) cancer drug or a cancer adjunctive or support therapy, and optionally the cancer drug or a cancer adjunctive or (as a drug or pharmaceutical) support therapy comprises (or further comprises, or comprises use of):

an anti-microtubule agent including at least one of, or any one of: a paclitaxel (e.g. TAXOL™ or GENEXOL™), a paclitaxel protein bound particles (e.g. ABRAXANE™), a polymeric micelle paclitaxel (GENEXOL PM™), a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B), a liposomal paclitaxel (e.g. LIPUSU™), a docetaxel (e.g., TAXOTERE™), a DHP107, an oral paclitaxel and P-gp inhibitor HM30181A (e.g. ORAXOL™), a polymeric micelle docetaxel (e.g. NANOXEL PM™), a cabazitaxel (e.g. JEVTANA ™), a polymeric micelle cabazitaxel, a vincristine, a vinblastine, a vinorelbine (e.g. NAVELBINE™), a vinflunine, and/or an eribulin (e.g. HALAVEN™), or any combination thereof,

an alkylating agent including at least one of, or any one of: a cisplatin (e.g. PLATINOL™), a carboplatin (e.g. PARAPLATIN™), oxaliplatin (e.g., ELOXATIN™), a NC-6004 (e.g. LIPOPLATIN ™), an oxaliplatin (e.g., ELOXATIN™), a bendamustine

(e.g., TREANDA™), a cyclophosphamide, an ifosfamide, a chlorambucil, a melphalan, a dacarbazine, a mitozalomide, and/or a temozolomide, or any combination thereof,

a cytotoxic antibiotic including at least one of, or any one of: a doxorubicin (e.g. ADRIAMYCIN™ or RUBEX™), a pegylated liposomal doxorubicin (e.g. DOXIL™ or LIPODOX™), a non-pegylated liposomal doxorubicin (e.g. MYOCET™), a polymeric micelle doxorubicin, a daunorubicin, a liposomal daunorubicin, an epirubicin (e.g. ELLENCE™), an idararubicin, a piranubicin, an aclarubicin, a mitoxantrone, a bleomycin, and/or a mitomycin, or any combination thereof,

a topisomerase inhibitor including at least one of, or any one of: an irinotecan (e.g., CAMPTOSAR™), a liposomal irinotecan (e.g., ONIVYDE™), an etirinotecan pegol, (e.g. ONZEALD™), a liposomal encapsulated irinotecan and 5FU (e.g. CPX-1), a topotecan, a camptothecin and/or an etoposide (e.g. ETOPOPHOS™), or any combination thereof,

an anti-metabolite including at least one of, or any one of: a methotrexate, a pemetrexed (e.g. ALIMTA™), a pralatrexate (e.g. FOLOTYN™), a 5-fluorouracil or 5-FU (e.g. ADRUCIL™), a capecitabine (e.g., XELODA™), a tegafur/gimeracil/oteracil (e.g. TEYSUNO™ or S-1™), a trifluridine/tipiracil (e.g. LONSURF™), a gemcitabine (e.g. GEMZAR™), a NUC-1031 (e.g. ACELARIN™), and/or a azacytidine (e.g. VIDAZA™) and a hydroxycarbamide, or any combination thereof,

a cisplatin and a pemetrexed, or a carboplatin and a pemetrexed,

a cisplatin and paclitaxel; a cisplatin and a paclitaxel protein bound particles; a cisplatin and a polymeric micelle paclitaxel (GENEXOL PM™); a cisplatin and a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); and/or a cisplatin and a liposomal paclitaxel, (e.g. LIPUSU™),

a carboplatin and paclitaxel; a carboplatin and a paclitaxel protein bound particles; a carboplatin and a polymeric micelle paclitaxel (GENEXOL PM™); a carboplatin and a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); and/or, a carboplatin and a liposomal paclitaxel, (e.g. LIPUSU™),

an oxaliplatin and paclitaxel; an oxaliplatin and a paclitaxel protein bound particles; an oxaliplatin and a polymeric micelle paclitaxel (GENEXOL PM™); an oxaliplatin and a polymeric micelle paclitaxel manufactured by Shanghai Yizhong

Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); and/or, an oxaliplatin and a liposomal paclitaxel, (e.g. LIPUSU™);

a polymeric micelle doxorubicin and a paclitaxel protein bound particle; a cisplatin and a polymeric micelle paclitaxel (GENEXOL PM™); a cisplatin and a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); and/or a cisplatin and a liposomal paclitaxel, (e.g. LIPUSU™);

a gemcitabine and paclitaxel; a gemcitabine and a paclitaxel protein bound particles; a gemcitabine and a polymeric micelle paclitaxel (GENEXOL PM™); a gemcitabine and a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); a gemcitabine and a liposomal paclitaxel, (e.g. LIPUSU™); a gemcitabine and a carboplatin, a gemcitabine and an oxaliplatin; and/or a gemcitabine and a NC-6004,

a gemcitabine, a paclitaxel and a cisplatin; a gemcitabine, a paclitaxel protein bound particles and a cisplatin; a gemcitabine, a polymeric micelle paclitaxel (GENEXOL PM™) and a cisplatin; a gemcitabine, a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B) and a cisplatin; and/or a gemcitabine, a liposomal paclitaxel, (e.g. LIPUSU™) and a cisplatin,

a gemcitabine, a paclitaxel and a NC-6004; a gemcitabine, a paclitaxel protein bound particles and a NC-6004; a gemcitabine, a polymeric micelle paclitaxel (GENEXOL PM™) and a NC-6004; a gemcitabine, a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B) and a NC-6004; and/or a gemcitabine, a liposomal paclitaxel, (e.g. LIPUSU™) and a NC-6004;

a "FOLFIRI" treatment (a combination of folinic acid, or leucovorin, a vitamin B derivative; 5-flurouracil; irinotecan, optionally with liposomal irinotecan);

a "FOLFOX" treatment (a combination of folinic acid, or leucovorin; 5-fluorouracil; oxaliplatin);

a "FOLFIRINOX" treatment (a combination of folinic acid, or leucovorin; irinotecan, optionally with liposomal irinotecan; oxaliplatin)

a calcitriol (also called 1,25-dihydroxycholecalciferol), or a ROCALTROL™, CALCIJEX™, or a DECOSTRIOL™,

a tyrosine kinase inhibitor (TKI), and optionally the TKI comprises a sorafenib (e.g. NEXAVAR™), regorafenib (e.g. STIVARGA™), levantinib (e.g., LENVIMA™), cabozanitinib (e.g., CABOMETYX™, COMETRIQ™), ibrutinib (e.g. IMBRUVICA™), afatinib, axitinib, cabimetinib, crizotinib, eradafitinib, erlotinib, gefitinib, lapatinib, pazopanib, sunitinib, vandetantib, vemuraferib, apatinib, savolitinib, fruquinitinib, sulfatinib, epitinib, theliatinib, lifirafenib, zanubrutinib, ivosidenib, avapritinib, CS3006, CS3008, CS3009, CBT101, CBT102, or any combination thereof,

a PARP inhibitor (inhibitors of the enzyme poly ADP ribose polymerase), optionally olaparib (LYNPARZA™); rucaparib (e.g., RUBRACA™); niraparib (e.g., ZEJULA™); talazoparib; fluzoparib; AZD2281 (e.g., OLAPARIB™); ABT-888 (e.g., VELIPARIB™); AG014699 (e.g., RUCAPARIB™), simmiparib, SC-10914, CEP-8983, and/or pamiparib, or any combination thereof,

a Programmed cell death protein 1 (PD1) inhibitor, optionally a nivolumab (e.g., OPDIVO™); pembrolizumab (e.g., KEYTRUDA™), cemiplimab, genolimzumab, dostarlimab, PDR001, AMP-224; LZM-009; BL-754091; JNJ-63723283; AJ0103; AGEN-2034; JS001; tislelizumab; MGA-012; GLS-010; SHR-120; CK-301; HTI-1316; JS001; IBI308; KN035; CS1003; CBT-501 and/or BAT-1306, or any combination thereof,

a Programmed death-ligand 1 (PDL1) inhibitor, optionally atezolizumab (e.g., TECENTRIQ™); avelumab (e.g., BAVENCIO™); durvalumab (e.g., IMFINZI™); LY-3300054;CX-072; FAZ-053; SHR-1316; TQB2450; LZM009; KL-A167; STI-A1014; AK104; HLZ-10; BGB-A333; MSB-2311; HLX-20; CS1001; CBT-502; KN-035; and/or WBT3155, or any combination thereof,

a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, and optionally the CTLA-4 inhibitor comprises: ipilimumab (e.g., YERVOY™); tremelimumab; JS007; CS3002 ; and/or CBT-509, or any combination thereof,

a cisplatin, pemetrexed and a Programmed cell Death protein 1 (PD1) inhibitor, and optionally the PD1 inhibitor comprises: nivolumab; pembrolizumab; cemiplimab; genolizmzumab; dostarlimab; PDR001; AMP-224; LZM-009; BL-754091; JNJ-63723283; AJ0103; AGEN-2034; JS001; tislelizumab; MGA-012; GLS-010; SHR-120; CK-301; HTI-1316; JS001; IBI308; KN035; CS1003; CBT-501 and/or BAT-1306, or any combination thereof,

a cisplatin, a pemetrexed and a programmed death-ligand 1 (PDL1) inhibitor, and optionally the PDL1 inhibitor comprises: atezolizumab, avelumab, durvalumab, LY-3300054, CX-072, FAZ-053, SHR-1316, TQB2450, LZM009, KL-A167, STI-A1014, AK104, HLZ-10, BGB-A333, MSB-2311, HLX-20, CS1001, CBT-502, KN-035, and/or WBT3155, or any combination thereof;

a cisplatin, pemetrexed and a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, and optionally the CTLA-4 inhibitor comprises: ipilimumab, tremelimumab, JS007, CS3002, and/or CBT-509, or any combination thereof,

a carboplatin, a pemetrexed and a Programmed cell Death protein 1 (PD1) inhibitor, and optionally the PD1 inhibitor comprises: nivolumab, pembrolizumab, cemiplimab, genolizmzumab, dostarlimab, PDR001, AMP-224, LZM-009, BL-754091, JNJ-63723283, AJ0103, AGEN-2034, JS001, tislelizumab, MGA-012, GLS-010, SHR-120, CK-301, HTI-1316, JS001, IBI308, KN035, CS1003, CBT-501 and/or BAT-1306

a carboplatin, a pemetrexed and a programmed death-ligand 1 (PDL1) inhibitor, and optionally the PDL1 inhibitor comprises: atezolizumab, avelumab, durvalumab, LY-3300054, CX-072, FAZ-053, SHR-1316, TQB2450, LZM009, KL-A167, STI-A1014, AK104, HLZ-10, BGB-A333, MSB-2311, HLX-20, CS1001, CBT-502, KN-035, and/or WBT3155, or any combination thereof,

a carboplatin, a pemetrexed and a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, and optionally the CTLA-4 inhibitor comprises ipilimumab, tremelimumab, JS007, CS3002 , and/or CBT-509, or any combination thereof,

a polymeric micelle doxorubicin and a Programmed cell Death protein 1 (PD1) inhibitor, and optionally the PD1 inhibitor comprises: nivolumab, pembrolizumab, cemiplimab, genolizmzumab, dostarlimab, PDR001, AMP-224, LZM-009, BL-754091, JNJ-63723283, AJ0103, AGEN-2034, JS001, tislelizumab, MGA-012, GLS-010, SHR-120, CK-301, HTI-1316, JS001, IBI308, KN035, CS1003, CBT-501 and/or BAT-1306, or any combination thereof,

a polymeric micelle doxorubicin and a programmed death-ligand 1 (PDL1) inhibitor, and optionally the PDL1 inhibitor comprises: atezolizumab, avelumab, durvalumab; LY-3300054; CX-072; FAZ-053; SHR-1316; TQB2450; LZM009; KL-A167; STI-A1014; AK104; HLZ-10; BGB-A333; MSB-2311; HLX-20; CS1001; CBT-502; KN-035; and/or WBT3155, or any combination thereof,

a polymeric micelle doxorubicin and a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B) and a Programmed cell Death protein 1 (PD1) inhibitor, and optionally the PD1 inhibitor comprises: nivolumab, pembrolizumab, cemiplimab, genolizmzumab, dostarlimab, PDR001, AMP-224, LZM-009, BL-754091, JNJ-63723283, AJ0103, AGEN-2034, JS001, tislelizumab, MGA-012, GLS-010, SHR-120, CK-301, HTI-1316, JS001, IBI308, KN035, CS1003, CBT-501 and/or BAT-1306, or any combination thereof,

a polymeric micelle doxorubicin and a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B) and a programmed death-ligand 1 (PDL1) inhibitor, and optionally the PDL1 inhibitor comprises: atezolizumab, avelumab, durvalumab, LY-3300054, CX-072, FAZ-053, SHR-1316, TQB2450, LZM009, KL-A167, STI-A1014, AK104, HLZ-10, BGB-A333, MSB-2311, HLX-20, CS1001, CBT-502, KN-035, and/or WBT3155, or any combination thereof,

an anti-microtubule agent, wherein optionally, the anti-microtubule agent comprises a paclitaxel (e.g. TAXOL™ or GENEXOL™); a paclitaxel protein bound particles (e.g. ABRAXANE™); a polymeric micelle paclitaxel (GENEXOL PM™); a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); a liposomal paclitaxel, (e.g. LIPUSU™); a DHP107, an oral paclitaxel and P-gp inhibitor HM30181A (e.g. ORAXOL™), and a Programmed cell Death protein 1 (PD1) inhibitor, wherein optionally the PD1 inhibitor comprises nivolumab; pembrolizumab; cemiplimab; genolizmzumab; dostarlimab; PDR001; AMP-224; LZM-009; BL-754091; JNJ-63723283; AJ0103; AGEN-2034; JS001; tislelizumab; MGA-012; GLS-010; SHR-120; CK-301; HTI-1316; JS001; IBI308; KN035; CS1003; CBT-501 and/or BAT-1306, or any combination thereof,

an anti-microtubule agent, wherein optionally, the anti-microtubule agent comprises a paclitaxel (e.g. TAXOL™ or GENEXOL™); a paclitaxel protein bound particles (e.g. ABRAXANE™); a polymeric micelle paclitaxel (GENEXOL PM™); a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); a liposomal paclitaxel, (e.g. LIPUSU™); a DHP107, an oral paclitaxel and P-gp inhibitor HM30181A (e.g.

ORAXOL™) and a programmed death-ligand 1 (PDL1) inhibitor, wherein optionally the PDL1 inhibitor comprises atezolizumab; avelumab; durvalumab; LY-3300054; CX-072; FAZ-053; SHR-1316; TQB2450; LZM009; KL-A167; STI-A1014; AK104; HLZ-10; BGB-A333; MSB-2311; HLX-20; CS1001; CBT-502; KN-035; and/or WBT3155, or any combination thereof,

an anti-microtubule agent, wherein optionally the anti-microtubule agent comprises a paclitaxel (e.g. TAXOL™ or GENEXOL™); a paclitaxel protein bound particles (e.g. ABRAXANE™); a polymeric micelle paclitaxel (GENEXOL PM™); a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); a liposomal paclitaxel, (e.g. LIPUSU™), a DHP107, an oral paclitaxel and P-gp inhibitor HM30181A (e.g. ORAXOL™) or any combination thereof; and a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, wherein optionally the CTLA-4 inhibitor comprises ipilimumab; tremelimumab; JS007; CS3002 ; and/or CBT-509, or any combination thereof,

an anti-microtubule agents, wherein optionally the anti-microtubule agent comprises a paclitaxel (e.g. TAXOL™ or GENEXOL™); a paclitaxel protein bound particles (e.g. ABRAXANE™); a polymeric micelle paclitaxel (GENEXOL PM™); a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); a liposomal paclitaxel, (e.g. LIPUSU™), and an alkylating agent, wherein optionally the alkylating agent comprises a cisplatin, a carboplatin; oxaliplatin; a NC-6004, an oxaliplatin; and, a Programmed cell Death protein 1 (PD1) inhibitor, wherein optionally the PD1 inhibitor comprises nivolumab; embrolizumab; cemiplimab; genolizmzumab; dostarlimab; PDR001; AMP-224; LZM-009; BL-754091; JNJ-63723283; AJ0103; AGEN-2034; JS001; tislelizumab; MGA-012; GLS-010; SHR-120; CK-301; HTI-1316; JS001; IBI308; KN035; CS1003; CBT-501 and/or BAT-1306, or any combination thereof,

an anti-microtubule agent, wherein optionally the anti-microtubule agent comprises a paclitaxel (e.g. TAXOL™ or GENEXOL™); a paclitaxel protein bound particles (e.g. ABRAXANE™), or any combination thereof; a polymeric micelle paclitaxel (GENEXOL PM™); a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B); a liposomal paclitaxel, (e.g. LIPUSU™), and alkylating agents optionally, a cisplatin;

or optionally a carboplatin; oxaliplatin; a NC-6004; an oxaliplatin; and a programmed death-ligand 1 (PDL1) inhibitor, wherein optionally the PDL1 inhibitor comprises atezolizumab; avelumab; durvalumab; LY-3300054; CX-072; FAZ-053; SHR-1316; TQB2450; LZM009; KL-A167; STI-A1014; AK104; HLZ-10; BGB-A333; MSB-2311; HLX-20; CS1001; CBT-502; KN-035; and/or WBT3155, or any combination thereof,

an anti-microtubule agent, wherein optionally the anti-microtubule agent comprises a paclitaxel (e.g. TAXOL™ or GENEXOL™), a paclitaxel protein bound particles (e.g. ABRAXANE™), a polymeric micelle paclitaxel (GENEXOL PM™), a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B), a liposomal paclitaxel, (e.g. LIPUSU™), or any combination thereof; and an alkylating agent, wherein optionally the alkylating agent comprises a cisplatin,, a carboplatin, oxaliplatin, a NC-6004, an oxaliplatin; and, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, wherein optionally the CTLA-4 inhibitor comprises ipilimumab; tremelimumab; JS007; CS3002 ; and/or CBT-509, or any combination thereof,

a treatment or amelioration for a neuroendocrine tumor or a carcinoid or a side effect caused by the carcinoid or neuroendocrine tumor; optionally, a drug that is an analog of somatostatin such as e.g., the peptide H-D-2Nal-Cys(1)-Tyr-D-Trp-Lys-Val-Cys(1)-Thr-NH2, or lanreotide or lanreotide acetate or lanreotide SR (e.g., SOMATULINE™), manufactured e.g., by Ipsen (Paris, France); or, octreotide (e.g., SANDOSTATIN™) or octreotide acetate LAR (SANDOSTATIN LAR™, Novartis Pharma AG), or any combination thereof;

and optionally the cancer drug or a cancer adjunctive or (as a drug or pharmaceutical) support therapy is formulated with the first formulation and/or the second formulation, or the cancer drug or a cancer adjunctive or (as a drug or pharmaceutical) support therapy is separately formulated, for example, the cancer drug or a cancer adjunctive or (as a drug or pharmaceutical) support therapy is formulated in the form of a tablet, pill, geltab, capsule and the like which is placed or inserted in the same compartment on a blister card, clamshell or tray or equivalent with one or more tablets, pills, geltabs, capsules and the like comprising a first formulation and/or second formulation as provided herein, wherein all tablets, pills, geltabs, capsules and the like in the same compartment are to be taken at the same time by the user, e.g., a patient.

In alternative embodiments, provided are Uses of the therapeutic combination of any of the preceding claims, in the manufacture of a medicament for treating or ameliorating a cancer, tumor or a dysfunctional cell condition, or a symptom of cancer, tumor or a dysfunctional cell condition.

In alternative embodiments, provided are pharmaceutical dosage form, a drug delivery device or package, a blister package, a clamshell or a tray, or a product of manufacture as provided herein, for use in treating or ameliorating a cancer, tumor or a dysfunctional cell condition, or a symptom of cancer, tumor or a dysfunctional cell condition.

In alternative embodiments of the Uses or the pharmaceutical dosage forms, or the drug delivery devices or packages, blister packages, clamshells or trays, or the products of manufacture as set forth herein, wherein the cancer or tumor or dysfunctional cell condition(s) is or are: neuroendocrine tumors, cancers of the endocrine system, and pancreatic cancer, including gastroenteropancreatic neuroendocrine tumors (GEP-NET), pancreatic neuroendocrine tumors (PanNETs), islet cell tumors or non-islet hypoglycemic cell tumor, intestinal endocrine tumors, carcinoids, adenocarcinoma pancreatic tumors, pheochromocytoma (PCC) or cancer of the adrenal gland, or cancer of the medulla of the adrenal glands, paraganglioma or chemodectoma, a gastrinoma (a gastrin secreting tumor), primary neuroendocrine carcinoma of the skin; hepatocellular carcinoma and liver cancers; brain and nerve cell cancers including neuroblastomas, brain stem glioma and glioblastoma multiforme; ovarian cancer; angiosarcoma; bone cancer and osteosarcoma; sarcomas, including bone and soft tissue sarcomas, chondrosarcoma, liposarcoma, rhabdomyosarcoma, Kaposi’s sarcoma, desmoid tumor, epithelioid sarcoma, lymphangiosarcoma, and lymphosarcoma; familial adenomatous polyposis; lung cancers including small cell lung cancer and non-small cell lung cancer; skin cancer and melanomas, including cutaneous or intraocular melanoma, merkel-cell carcinoma (MCC); cancers of the head and neck; uterine cancer; rectal and colorectal cancer, including colon cancer and cancer of the anal region; stomach cancer; breast cancer; carcinoma of the fallopian tubes; carcinoma of the endometrium; carcinoma of the cervix; carcinoma of the vagina; carcinoma of the vulva; lymphomas, including chronic or acute leukemia, lymphocytic lymphomas, Hodgkin's Disease, primary CNS lymphoma; cancer of the esophagus; cancer of the small intestine; cancer of the thyroid gland or parathyroid gland, medullary thyroid cancer (MTC) or cancer of the parafollicular cells (C cells); cancer of

the urethra; cancer of the penis; prostate cancer; cancer of the bladder; cancer of the kidney or ureter or renal cell carcinoma, or carcinoma of the renal pelvis; a neoplasm of the central nervous system (CNS); spinal axis tumors; pituitary adenoma; and, retinoblastoma; and any combination thereof.

The details of one or more aspects of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

All publications, patents and patent applications cited herein are hereby expressly incorporated by reference for all purposes.

DESCRIPTION OF DRAWINGS

The drawings set forth herein are illustrative of exemplary embodiments provided herein and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. 1 graphically illustrates the concept of an inverted dose response, as discussed in further detail, below.

FIG. 2 schematically illustrates an exemplary drug delivery device, blister package, clamshell or tray as provided herein, as discussed in further detail, below.

FIG. 3 and FIG. 4 schematically illustrate a randomized, double-blind, placebo-controlled two-staged study using the exemplary therapeutic combination VT-11CR with GemNab for untreated, metastatic pancreatic cancer, as described in detail in Example 2, below.

FIG. 5 graphically illustrates overall survival of GemNab ± propranolol and etodolac in patients with locally advanced / metastatic pancreatic cancer in the studies illustrated in FIG. 3 and FIG. 4, as described in detail in Example 2, below.

FIG. 6 schematically illustrates a two-staged study using the exemplary therapeutic combination VT-11CR with paclitaxel and gemcitabine for metastatic adenocarcinoma, as described in detail in Example 2, below.

FIG. 7 graphically illustrates data demonstrating that propranolol and/or etodolac show inverted dose responses in immunocompetent animal models B16F10 melanoma in mice (for a propranolol study) (graph on left) and hepatocellular carcinoma (HCC) in Shionogi mice (for etodolac) (right graph).

FIG. 8, FIG. 9, FIG. 10 and FIG. 11 graphically illustrate dissolution profiles of propranolol (individual product) at 5ºC / ambient RH, 25ºC / 60% RH, 30 ºC / 65% RH and 40ºC /75% RH (relative humidity), as described in detail in Example 3, below.

FIG. 12 graphically illustrates a dissolution profile of propranolol at =0, 9-month 5° C / ambient RH and 9-month 25 ºC / 60% RH, as described in detail in Example 3, below.

FIG. 13, FIG. 14, FIG. 15 and FIG. 16 graphically illustrate dissolution profiles of propranolol (solid lines) and etodolac (dashed lines) at 5 ºC / ambient RH, 25 ºC / 60% RH, 30 ºC / 65% RH and 40 ºC / 75% RH, as described in detail in Example 3, below.

FIG. 18 illustrates in tabular form the dissolution profile of Propranolol HCl, 16 mg IR and 16 mg DR, in combination with Etodolac 70 mg – specifically observing the 240 minutes – 360 minutes on stability up to 6 months.

FIG. 19 schematically illustrates an exemplary universal multi-drug delivery system as provided herein, where a week of pharmaceutical dosage forms are stored on four rows, two rows for administration for morning or breakfast, or AM administration, and two rows are for evening, dinnertime or PM administration, as discussed in detail, below.

Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

In alternative embodiments, provided are therapeutic combinations, pharmaceutical compositions, formulations, kits and devices for treating, preventing or ameliorating a tumor or a cancer, and methods for treating, preventing or ameliorating a tumor or a cancer. In alternative embodiments, provided are therapeutic combinations, pharmaceutical compositions, formulations, kits and devices comprising: a beta adrenergic receptor antagonist (a “beta blocker”); and, a non-steroidal anti-inflammatory drug (a NSAID), formulated and packaged for chronodosed and pulsatile release.

In alternative embodiments, provided are therapeutic combinations, pharmaceutical compositions, formulations, kits and devices as provided herein are designed to exploit an inverted dose response, as illustrated in FIG. 1, using: a fixed dose combination capsule; delayed or controlled release (DR) microparticles or microbeads (e.g., as in Level 1 VT-11CR AM or which comprises a formulation of polysaccharide microbeads or microparticles coated with propranolol and EUDRAGIT® polymer and

etodolac power with excipients (see Table 1, below); and, as in Level 2 VT-11CR PM capsules which is comprised of a formulation of etodolac (as the only active ingredient, i.e., no propranolol) and excipients as listed in Table 2, below); low non-standard dose strengths; optimized non-standard timing, with propranolol (e.g., INDERAL™) in the daytime (e.g., in the morning, at breakfast or afternoon) only, and optionally also with etodolac in the morning, and etodolac in the evening (e.g., at bed-time, dinnertime, in the PM) alone. In alternative embodiments, the therapeutic combinations, pharmaceutical compositions or formulations are packaged in blister cards or equivalents for easy titration, dosage modification and adherence.

In alternative embodiments, therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein comprise an easy to use blister card with a seven day supply, with a spare, of propranolol (including e.g., a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof) and etodolac (including e.g., a racemic R(+) and S(–) mixture of etodolac, a substantially pure (S)-enantiomer of etodolac, or a pharmaceutically acceptable salt thereof, or mixtures thereof), e.g., as illustrated in FIG. 2, wherein:

- the packaging of the therapeutic combinations, pharmaceutical compositions, formulations for morning (or AM) administration include: one, two or three (or more) tablets, pills, capsules, geltabs or equivalents comprising: immediate release (IR) propranolol powder, particles or equivalent IR formulation; and delayed (or controlled) release (DR) propranolol particles or equivalent DR formulation, and IR etodolac powder, particles or equivalent IR formulation,

wherein optionally each morning (or AM) administration is contained in one compartment of a blister card or equivalent, and arranged on the blister card or equivalent as an AM dosage, versus an evening dose; and,

- the packaging of the therapeutic combinations, pharmaceutical compositions, formulations for evening or bed-time (e.g., dinnertime or PM) administration include: one, two or three (or more) tablets, pills, capsules, geltabs or equivalents comprising IR etodolac powder, particles or equivalent IR formulation,

wherein optionally each evening or bed-time (e.g., dinnertime or PM) administration is contained in one compartment of a blister card or equivalent, and arranged on the blister card or equivalent as a PM dosage, versus an AM dose.

In summary, for this exemplary embodiment, the therapeutic combination, pharmaceutical composition, formulation and kits as provided herein are packaged in easy to use "titration packages", such as blister cards or equivalents, having one, two or three (or more) tablets, pills, capsules, geltabs or equivalents in the morning (or AM), and one, two or three (or more) tablets, pills, capsules, geltabs or equivalents in the evening or bedtime (or dinnertime or PM).

In alternative embodiments, the therapeutic combination comprises:

- a low dose of one, two or three (or more) tablets, pills, capsules, geltabs or equivalents for administration in the morning, or breakfast or AM, that comprises: about 4 to 32, 8 to 24, 12 to 20, 14 to 18 or 15 to 17 mg of IR propranolol hydrochloride; about 4 to 32, 8 to 24, 12 to 20, 14 to 18 or 15 to 17 mg of DR propranolol hydrochloride; and about 0 to 180, 40 to 120, 60 to 100, 65 to 80 mg IR etodolac, or

- a high dose of one, two or three (or more) tablets, pills, capsules, geltabs or equivalents for administration in the morning, or breakfast or AM, that comprises: about 8 to 64, 16 to 48, 24 to 40, 28 to 36 or 30 to 34 mg of IR propranolol hydrochloride; about 8 to 64, 16 to 48, 24 to 40, 28 to 36 or 30 to 34 mg of DR propranolol hydrochloride; and about 0 to 360, 80 to 240, 120 to 200, 130 to 160 mg IR etodolac,

and optionally the low dose of a morning tablet, pill or capsule has approximately equal amounts of IR and DR propranolol, e.g., 16 mg IR and 16 mg DR propranolol;

- one tablet, pill, capsule or equivalent for administration in the evening or bedtime (e.g., PM) having between about 200 and 400 mg, between about 250 and 300 mg, about 270 mg, or about 340 mg, IR etodolac, wherein in one embodiment the evening or bedtime IR 270 mg formulation of etodolac is designated "VT-11CR PM");

and in one embodiment, when one tablet, pill, capsule or equivalent is formulated or designated for administration in the morning, or AM, and comprises a total dosage of:

16 mg of IR propranolol hydrochloride; 16 mg of DR propranolol hydrochloride; and 70 mg IR etodolac, the therapeutic combination is designated "Level 1 VT-11CR AM" (for example, see Example 1, below, where "low dose cards" comprise a one morning (AM) blister strip containing 8 VT-11CR capsules and one evening (PM) blister strip containing 8 etodolac capsules);

and in one embodiment, when one or two tablet(s), pill(s), capsule(s) or equivalent is/are formulated or designated for administration in the morning, or AM, and comprise a total dosage of: 32 mg of IR propranolol hydrochloride; 32 mg of DR propranolol hydrochloride; and 140 mg IR etodolac, the therapeutic combination is designated "Level 2 VT-11CR AM" (for example, see Example 1, below, where "high dose cards" are comprised of two morning (AM) blister strips containing a total of 16 VT-11CR capsules and two evening (PM) blister strips containing a total of 16 etodolac capsules).

In alternative embodiments, the therapeutic combination comprises:

- one tablet, pill, capsule or equivalent for administration in the morning, or AM, that comprises: about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of IR propranolol hydrochloride; about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of DR propranolol (e.g., propranolol hydrochloride),

and optionally the morning tablet has approximately equal amounts of IR and DR propranolol, e.g., 16 mg IR and 16 mg DR propranolol (e.g., propranolol hydrochloride);

- one tablet, pill, capsule or equivalent for administration in the afternoon or evening (e.g., PM) having between about 200 and 400 mg, between about 250 and 300 mg, about 270 mg, or about 340 mg, IR etodolac;

In alternative embodiments, the therapeutic combination comprises dose ranges and percent release splits comprise release profiles, where for propranolol: 35% to 60% of the administered dosage is released in the morning (AM) and 40% to 65% is released in the afternoon; and for etodolac, 0 to 30% of the administered dosage is released in the morning (AM) and 70% to 100% is released in the afternoon or evening (PM).

In alternative embodiments, the therapeutic combination comprises dosage amounts that target release of high amounts of propranolol in the AM, e.g., 64 mg propranolol and release of high amounts of etodolac in the PM, e.g., 680 mg etodolac.

In alternative embodiments, the therapeutic combination comprises dosage amounts that target release of, or administration of, 32 mg propranolol in the AM and 340

mg etodolac in the PM. In alternative embodiments, the therapeutic combination comprises dosage amounts that target release of, or administration of, 32 mg propranolol in the AM and 680 mg etodolac in the PM. In alternative embodiments, the therapeutic combination comprises dosage amounts that target release of, or administration of, 64 mg propranolol in the AM and 340 mg etodolac in the PM. In alternative embodiments, equal amounts IR and DR are administered.

In alternative embodiments, the therapeutic combination comprises dosage amounts that include a higher dose range for propranolol, e.g., a total of between about 80 and 110 mg, or about 96 mg (e.g., equal amounts IR and DR) administered in the AM (or breakfast, or afternoon).

In alternative embodiments, the therapeutic combination comprises a substantially pure (S)-enantiomer (versus a racemic mixture) of propranolol, and in these embodiments dosages of propranolol is lowered by as much as half, or less. In alternative embodiments, the therapeutic combination comprises a substantially pure (S)-enantiomer (versus a racemic mixture) of etodolac, and in these embodiments dosages of propranolol can be lowered by as much as half, or less. For example, in alternative embodiments using a substantially pure (S)-enantiomer of propranolol, the therapeutic combination comprises dosage amounts that target release of, or administration of about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 total mg propranolol (including e.g., equal amounts of IR and DR formulations) in the AM, and etodolac in the PM. In another alternative embodiment using a substantially pure (S)-enantiomer of etodolac, the therapeutic combination comprises dosage amounts that target release of, or administration of etodolac is halved to about 10 to 100 mg of IR etodolac in the AM and between about 200 to 300 mg IR etodolac in the PM, or evening or dinnertime. In alternative embodiments, equal amounts IR and DR propranolol are administered. In alternative embodiments, low dosage administration of propranolol and/or etodolac take advantage of their inverted dose-responses to maximize efficacy and safety, as graphically illustrated e.g., in FIG. 7, which shows data demonstrating that propranolol and/or etodolac show inverted dose responses in immunocompetent animal models B16F10 melanoma in mice (for a propranolol study) and hepatocellular carcinoma (HCC) in Shionogi mice (for etodolac).

In alternative embodiments, the therapeutic combination comprises another beta blocker at the same effective dosage in place of propranolol, or comprises another beta

blocker in combination with propranolol adding up the same effective dosage as the exemplary formulations provided herein. In alternative embodiments, the other or additional beta blocker comprises for example: timolol (e.g., BETIMOL™), bupranolol, nadolol (e.g., CORGARD™), or, the other or additional beta blocker comprises a selective adrenergic beta-2 receptor inhibitor such as butoxumine or 3-(isopropylamino)-1-[(7-methyl-4-indanyl)oxy]butan-2-ol (also called ICI-118,551).

In alternative embodiments, the therapeutic combination comprises in place of etodolac another NSAID or another coxib at the same or equivalent dosage, or comprises another NSAID or another coxib in combination with etodolac adding up the same effective dosage as the exemplary formulations provided herein. In alternative embodiments, the other or additional NSAID or coxib comprises for example: imrecoxib; apricoxib; nimesulide; diclofenac (e.g., CATAFLAM™, VOLTAREN™); sulindac (e.g., CLINORIL™); meloxicam (e.g., MOBIC™, METACAM™), polmacoxib or CG100649 (e.g., ACELEX™), or a microsomal PGE-2 synthase inhibitor such as e.g., NX-580, and the like.

While the invention is not limited by any particular mechanism of action, a rational for the exemplary propranolol and etodolac therapeutic combinations as provided herein is driven by the recent advances in understanding the tumor biology including the macrophage contribution to the inflammatory component which promotes tumor growth, metastases, immune evasion and a negative impact on Natural Killer (NK) cell and T-lymphocyte (e.g., CTLs) anti-tumor functions. As individual agents both etodolac and propranolol have demonstrated the ability to repolarize the macrophages from an M2 to a M1 phenotype. M1 macrophages inhibit cancer growth and metastasis, stimulate immune function, co-ordinate the anti-cancer Th1 response and inhibit angiogenesis; while the M2 macrophages can suppress immune function, promote cancer growth and the Th2 inflammatory response and support angiogenesis. *In vivo* model systems in the cancer setting have confirmed the individual agents and the combination to be of benefit in terms of impact on immune function and outcomes. Exemplary propranolol and etodolac therapeutic combinations as provided herein, e.g., VT-11CR, inhibit both the adverse beta-adrenergic and prostaglandin signaling to reverse pro-tumor polarization of macrophages with a cascading potential effect on NK-cells and cytotoxic T-cells.

In alternative embodiments, the therapeutic combination comprises the "VT-11CR drug product", which consists of two individual dosage forms: a VT-11CR AM capsule and a VT-11CR PM capsule. In alternative embodiments, a VT-11CR AM capsule for oral administration combines two active ingredients: propranolol hydrochloride, a beta-adrenergic blocking agent, and etodolac, a NSAID. The VT-11CR AM capsule, 32/70 mg, contains 32 mg propranolol hydrochloride (as 16 mg immediate release (IR) beads and 16 mg delayed (or controlled) release (DR) beads), and 70 mg etodolac immediate release (IR) drug product. The VT-11CR PM capsule for oral administration contains one active ingredient: etodolac. The VT- 11CR PM capsule, 270 mg, contains 270 mg etodolac IR drug product. The quantitative composition of a VT-11CR AM capsule is presented in Table 1.

Table 1: Quantitative composition of VT-11CR AM capsules

Component	Quality Standard	Function	Amount (mg)
Propranolol HCl	USP	API	32.00
Sugar spheres PF006	NF	Core ingredient	152.78
Hypromellose	USP	Coating agent	8.00
Opadry clear	Proprietary[1]	Coating agent	9.64
Talc	USP	Basis for powder	18.25
Triethyl citrate	NF	Coating agent	6.07
Ammonio methacrylate copolymer dispersion Type A	NF	Coating agent	0.30
Ammonio methacrylate copolymer dispersion Type B	NF	Coating agent	30.06
Etodolac	USP	API	70.00
Microcrystalline cellulose	NF	Filler	14.48
Croscarmellose sodium	NF/EP	Disintegrant	9.55
Colloidal silicon dioxide	NF/EP	Glidant	0.95
Magnesium stearate	NF	Lubricant	0.48

White opaque CONI-SNAP™ hard gelatin capsule, size "0"	NF/USP	Encapsulation	1 unit
Total	352.56		
USP = United States Pharmacopoeia, NF = National Formulary, EP = European Pharmacopoeia			

[1] The film coating agent used in manufacture of propranolol HCl IR beads is OPADRY CLEAR™ (Colorcon, Inc., Harleysville, PA).

The quantitative composition of a VT-11CR PM capsule is presented in Table 2:

Table 2: Quantitative composition of VT-11CR PM capsules

Component	Quality Standard	Function	Amount (mg)
Etodolac	USP	API	270.00
Microcrystalline cellulose	NF	Filler	55.86
Croscarmellose sodium	NF/EP	Disintegrant	36.82
Colloidal silicon dioxide	NF/EP	Glidant	3.68
Magnesium stearate	NF	Lubricant	1.84
White opaque CONI-SNAP™ hard gelatin capsule, size "0"	NF/USP	Encapsulation	1 unit
Total	352.56		
USP = United States Pharmacopoeia, NF = National Formulary, EP = European Pharmacopoeia			

Dosing Regimens

Provided herein are novel formulations and dosaging regiments that solve existing problems when using the therapeutic combination of coxibs and beta blockers, for example: these problems can comprise side effects that limit the ability to chronodose the co-administration of beta blockers and coxibs; the complexity of the titration of individual pills needed to determine a tolerable dose limits their use and efficacy; and, it is difficult

to get patients to comply or adhere to a TID (three times a day) or more dosing regimen. Current dosage regimens of coxibs and beta blockers are formulated and dosaged for at least three times a day (tid), which is impractical in a community environment (e.g., patients unsupervised at home when self-administering), versus a clinical trials, setting.

The inventors used novel approaches to solve these problems, for example:

1. Dose level and timing based on modified 3+3 dosing finding studies where dose established was based on increasing dose if > 86.6% of cohort is tolerant, reducing dose if less than 50% of cohort is tolerant, and dose reached if 50% to 86.6% of cohort tolerant. Dosing timing was based on weight averages of dose timing used in pancreatic cancer study.
2. Used fixed dose combination at a two dose level, e.g., as presented on a blister card or equivalent, to enable simple titration of therapy to a tolerable dose.
3. Used a controlled release capsule to eliminate difficult patient compliance level (e.g., to eliminate or greatly reduce the amount of non-compliant patients, currently an endemic, widespread and consistent problem) when a TID (three times a day) dosaging regimen is used (see, e.g., Coleman, et al, J Manag Care Pharm. 2012; vol 18(7):527-39).

For example, in a previous cachexia study in patients with non-small-cell-lung cancer (NSCLC) using etodolac and propranolol (NCT00527319): :

1. Three arm randomized studies for the treatment of cachexia: control, 400 mg etodolac and 800 mg/day etodolac and propranolol individually titrated from 40mg, 70mg to 120 mg per day:

Tolerant Count and Percentage

Propranolol	Etodolac	Count	Percent (Pct)	
40/20/10 in AM, Afternoon, PM	200mg in AM and PM only	10	100%	
60/40/20 in AM, Afternoon, PM	200mg in AM and PM only	8	80%	Optimal
Total		10		

Propranolol	Etodolac	Count	Pct

20/10/10 in AM, Afternoon, PM	400mg in AM and PM only	10	100%	
40/20/10 in AM, Afternoon, PM	400mg in AM and PM only	9	90%	Optimal
60/40/20 in AM, Afternoon, PM	400mg in AM and PM only	4	40%	
Total		10		

As another example, in previous a hepatocellular carcinoma (HCC) study using etodolac and propranolol (NCT01265576):

Two arm randomized study for treatment of HCC, control room vs individually titrationed etodolac from 200 mg in AM and PM to 300 mg/day in AM and PM and etodolac of 20 mg in AM and PM, 30 mg in AM and PM 40 mg in AM and PM:

Tolerant Count and Percentage

Propranolol	Etodolac	Count	Pct	
20mg in AM, and PM	200mg in AM, and PM	9	100%	
20mg in AM, and PM	300mg in AM, and PM	8	89%	
40mg in AM, and PM	300mg in AM, and PM	5	56%	Optimal
60mg in AM, and PM	300mg in AM, and PM	3	33%	
Total		9	100%	

As another example, in a previous prostate cancer study using etodolac and propranolol (NCT01857817):

Two arm study of control vs target high dose of propranolol 44mg in AM, 22mg in afternoon and etodolac 340mg in AM and 340 mg in PM:

Tolerant Count and Percentage

Propranolol	Etodolac	Count	Percent (Pct)	
66mg	680mg	16	76%	Optimal
Total		21		

Previous Investigator Led study of propranolol + etodolac + nab-paclitaxel + gemcitabine vs nab-paclitaxel alone for the treatment of advanced pancreatic cancer.

(Bhattacharyya 2015)

Dosing titration algorithm:

Propranolol: 20 mg in AM and 20 mg in afternoon increased to 40 mg AM and 40 mg in afternoon based on heart rate change.

Etodolac: at 600 mg in PM and dose titrated down if GI discomfort to 400 mg in PM or increased to 200 mg in AM and 600mg PM if pain exists in AM:

No Treatment related SAEs (serious adverse events) were reported .

All patients tolerated therapy for minimum of 4 months.

The treatment group showed an 8.3 increase in overall survival versus control and the survival benefit was consistent across subpopulations of patients.

Bhattacharyya 2015 Drug Splits
By Dosage Amounts

	Percentage Daily Dose		
Propranolol Dosage Amount	AM	Afternoon	PM
Low dose <64mg/day	50%	50%	0%
High dose >64mg/day	50%	50%	0%

	Percent of Daily Dose		
Etodolac Dosage Amount	AM	Afternoon	PM
Low Dose <680mg/day	0%	0%	100%
High Dose =>680mg/day	25%	0%	75%

VT-11CR daily dosing amounts is <= 20% difference of pilot study drug amounts:

a. VT-11CR propranolol low dose 32 mg/ pilot study minimum 40mg =20% difference
b. VT-11CR propranolol 64 mg/pilot study maximum 80mg=20% difference
c. VT-11CR etodolac 340mg vs pilot study of 400mg = 15% difference
d. VT-12CR etodolac 680mg vs pilot study maximum 800mg=15% difference

VT-11CR dosing split <= 20% of the difference with pilot study drug split:

a. VT-11CR propranolol vs pilot study split = less than 5% difference at all dose ranges,
b. VT-11CR etodolac vs pilot study split =
    a. Level 1 dose:
        1. AM dose, VT-11CR of 20% vs pilot study of 0%, a 20% difference.
        2. PM dose: VT-11CR of 80% vs pilot study of 100% = 20% difference
    b. Level 2 dose:
        1. AM Dose: VT-11CR of 20% vs pilot study of 25% = 5% difference;
        2. PM dose: VT-11CR of 80% vs pilot study of 75% = 7% difference.

Pilot study evaluated 5 dose combinations vs VT-11CR = 2 dose combination.

Pilot study required individual titration of up/down for etodolac and two escalations of up dosing with propranolol vs VT-11CR with one single step titration.

Pilot study required patients to adhere to TID dosing vs VT-11CR with BID.

Proof-of-Concept of VT-11CR Dosing Regimen

Simulation Data to establish efficacy of VT-11CR (Level 1 and Level 2 dosing) versus Bhattacharyya 2015 data:

VT-11CR dosage amounts and release profiles are predicted to offer equal or greater safety and efficacy than Bhattacharyya 2015 based on *in vitro* dissolution, *in vitro in vivo* correlations and comparison by pharmacokinetic simulations.

Based on the dosage amounts in VT-11CR, the simulation shows the propranolol and etodolac concentrations are within the 80% to 125% of AUC (area under curve) of the minimum and maximum dosages of Bhattacharyya 2015. VT-11CR's propranolol and etodolac have similar "drug-free" intervals (below an active concentration) compared

to Bhattacharyya 2015. In addition, the VT-11CR's etodolac has C_{max}, and t_{max} within 80% to 125% of the Bhattacharyya 2015.

The dissolution data shows VT-11CR propranolol AM releases occur in one hour and the afternoon release occurs over three hours. In contrast, Bhattaryya 2015 propanolol AM release occurs within ¼ hour of administration. As such, VT-11CR dosing has lower C_{max} and delayed t_{max} that minimizes the hypotensive risks compared to a spike in beta adrenergic blockade from immediate release propranolol.

Unlike the Bhattacharyya 2015 dosing algorithm, the VT-11CR dosing initiates all patients at Level 1 (low dosage) of propranolol and etodolac and then escalates all patients to Level 2 (high dosage) of propranolol and etodolac. Based on the data from the dose finding studies, the VT11CR dose escalation algorithm enables most patients to benefit from high dosage of propranolol and etodolac (e.g., 66 mg propranolol and 680 mg etodolac). In contrast, only 30% (6 of 20) patients in Bhattacharyya 2015 benefited from a dosages greater than 40 mg propranolol and 600 mg etodolac.

VT-11CR Dosing Regimen (level 1 and Level 2)

While adhering within 80% to 125% AUC of the minimum and maximum dosages with similar drug free-interval with Bhattacharyya 2015 and with potential for more patients to benefit from higher dosages propranolol and etodolac, VT-11CR improves titration by reducing the titration complexity from five to only two options and improves the ease of adherence by reducing dose frequency from three (TID) (including a difficult to adhere afternoon dose) to two (BID) doses per day, e.g., as depicted below:

Patient Adherence/ Dose Frequency

Titration Ease / options	Three	Two
Two		VT-11CR
Five	Pilot Study	

Thus, based on these studies, new dosaging, formulation and delivery regimens, including VT-11CR, were invented, as described herein, including, e.g.:

In alternative embodiments, one tablet, pill, capsule or equivalent is formulated or designated (e.g., packaged) for administration in the morning, or AM, and comprises a total dosage of: 16 mg of IR propranolol hydrochloride; 16 mg of DR propranolol

hydrochloride; and 70 mg IR etodolac, the therapeutic combination is designated "Level 1 VT-11CR AM" (for example, see Example 1, below, where "low dose cards" comprise a one morning (AM) blister strip containing 8 VT-11CR capsules and one evening (PM) blister strip containing 8 etodolac capsules).

In alternative embodiments, one or two tablet(s), pill(s), capsule(s) or equivalent is/are formulated or designated (e.g., packaged) for administration in the morning, or AM, and comprise a total dosage of: 32 mg of IR propranolol hydrochloride; 32 mg of DR propranolol hydrochloride; and 140 mg IR etodolac, the therapeutic combination is designated "Level 2 VT-11CR AM" (for example, see Example 1, below, where "high dose cards" are comprised of two morning (AM) blister strips containing a total of 16 VT-11CR capsules and two evening (PM) blister strips containing a total of 16 etodolac capsules).

In alternative embodiments, one tablet, pill, capsule or equivalent is formulated or designated (e.g., packaged) for administration in the evening or bedtime (e.g., PM) having between about 200 and 400 mg, between about 250 and 300 mg, about 270 mg, or about 340 mg, IR etodolac, wherein in one embodiment the evening or bedtime IR 270 mg formulation of etodolac is designated "VT-11CR PM").

Methods of Treatment

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein are used for primary or supportive treatment of a cancer, wherein the treatment of a cancer can be a drug treatment or other therapy such as radiotherapy or a surgery. In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein are administered before, during and/or after the cancer treatment, e.g., the drug treatment, surgery and/or radiotherapy.

In alternative embodiments, the cancer is a dysfunctional cell condition. In alternative embodiments, the cancer or dysfunctional cell condition comprises (is) any metastatic or benign tumor, and the methods or uses as provided herein are used for ameliorating, treating (killing, eliminating, stopping the growth and/or metastasis of) dysfunctional cell conditions, cancer stem cells or cancer cells from: neuroendocrine tumors, cancers of the endocrine system, and pancreatic cancer, including gastroenteropancreatic neuroendocrine tumors (GEP-NET), pancreatic neuroendocrine

tumors (PanNETs), islet cell tumors or non-islet hypoglycemic cell tumor, intestinal endocrine tumors, carcinoids, adenocarcinoma pancreatic tumors, pheochromocytoma (PCC) or cancer of the adrenal gland, or cancer of the medulla of the adrenal glands, paraganglioma or chemodectoma, a gastrinoma (a gastrin secreting tumor), primary neuroendocrine carcinoma of the skin; hepatocellular carcinoma and liver cancers; brain and nerve cell cancers including neuroblastomas, brain stem glioma and glioblastoma multiforme; ovarian cancer; angiosarcoma; bone cancer and osteosarcoma; sarcomas, including bone and soft tissue sarcomas, chondrosarcoma, liposarcoma, rhabdomyosarcoma, Kaposi's sarcoma, desmoid tumor, epithelioid sarcoma, lymphangiosarcoma, and lymphosarcoma; familial adenomatous polyposis; lung cancers including small cell lung cancer and non-small cell lung cancer; skin cancer and melanomas, including cutaneous or intraocular melanoma, merkel-cell carcinoma (MCC); cancers of the head and neck; uterine cancer; rectal and colorectal cancer, including colon cancer and cancer of the anal region; stomach cancer; breast cancer; carcinoma of the fallopian tubes; carcinoma of the endometrium; carcinoma of the cervix; carcinoma of the vagina; carcinoma of the vulva; lymphomas, including chronic or acute leukemia, lymphocytic lymphomas, Hodgkin's Disease, primary CNS lymphoma; cancer of the esophagus; cancer of the small intestine; cancer of the thyroid gland or parathyroid gland, medullary thyroid cancer (MTC) or cancer of the parafollicular cells (C cells); cancer of the urethra; cancer of the penis; prostate cancer; cancer of the bladder; cancer of the kidney or ureter or renal cell carcinoma, or carcinoma of the renal pelvis; a neoplasm of the central nervous system (CNS); spinal axis tumors; pituitary adenoma; and, retinoblastoma; and any combination thereof.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein are administered before, during or after a therapeutic administration of a dysfunctional cell condition therapy, or another cancer drug or a cancer adjunctive or support therapy.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises: calcitriol (also called 1,25-dihydroxycholecalciferol), or ROCALTROL™, CALCIJEX™, or DECOSTRIOL™.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer

drug or a cancer adjunctive or support therapy comprises: a gemcitabine-based therapy, e.g., gemcitabine (e.g., GEMZAR™) alone; gemcitabine and paclitaxel; gemcitabine, paclitaxel and platinum; gemcitabine and lipo-platinum (e.g., NC-6004, a micellar nanoparticle product of cisplatin); gemcitabine and capecitabine; gemcitabine and S1 (S1 is the combination drug tegafur/ gimeracil/ oteracil, trade name TEYSUNO™); and/or, a nucleoside analog of gemcitabine such as NUC-1031 (ACELARIN®).

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises: e.g., a 5-flurouracil (5-FU) based therapy, e.g., capecitabine (e.g., XELODA™) alone; "FOLFIRI" treatment (a combination of folinic acid, or leucovorin, a vitamin B derivative; 5-flurouracil; and, irinotecan (e.g., CAMPTOSAR™), a topoisomerase inhibitor), optionally with liposomal irinotecan (e.g., ONIVYDE™); "FOLFOX" treatment (a combination of folinic acid, or leucovorin, a vitamin B derivative; 5-flurouracil; and, oxaliplatin (e.g., ELOXATIN™); "FOLFIRINOX" treatment (a combination of folinic acid, or leucovorin, a vitamin B derivative; 5-flurouracil; irinotecan (e.g., CAMPTOSAR™), a topoisomerase inhibitor; and, oxaliplatin (e.g., ELOXATIN™)); the nucleoside analog of 5-FU NUC-3373; a recombinant human hyaluronidase enzyme (e.g. PEGPH20™); and/or tifluridine and/or tipiracil (e.g., LONSURF™).

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises: a tyrosine kinase inhibitor (TKI) such as sorafenib (e.g. NEXAVAR™), regorafenib (e.g. STIVARGA™), levantinib (e.g., LENVIMA™), cabozanitinib (e.g., CABOMETYX™, COMETRIQ™), ibrutinib (e.g. IMBRUVICA™), apatinibi and/or BGB-3111.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises: a PARP inhibitors (inhibitors of the enzyme poly ADP ribose polymerase), e.g., olaparib (LYNPARZA™); rucaparib (e.g., RUBRACA™); niraparib (e.g., ZEJULA™); talazoparib; fluzoparib; AZD2281 (e.g., OLAPARIB™); ABT-888 (e.g., VELIPARIB™); AG014699 (e.g., RUCAPARIB™), simmiparib, SC-10914, CEP-8983, and/or BGB-290.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises: a Programmed cell Death protein 1 (PD1) inhibitor, e.g., nivolumab (e.g., OPDIVO™); pembrolizumab (e.g., KEYTRUDA™); avelumab (e.g., BAVENCIO™); durvalumab (e.g., IMFINZI™); atezolizumab (e.g., TECENTRIQ™); BGB-A317; MGA012; GLS-010; SHR-120; CK-301 and/or HTI-1316.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises: a programmed death-ligand 1 (PDL1) inhibitor, e.g., atezolizumab (e.g., TECENTRIQ™); avelumab (e.g., BAVENCIO™); durvalumab (e.g., IMFINZI™); and/or HTI-1316.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises: a drug that inhibits cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), e.g., ipilimumab (e.g., YERVOY™) or tremelimumab.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises: an “immuno-oncology” therapy, including e.g., treatment for an oncolytic virus, or an autologous formula fixed tissue vaccine, or immune checkpoint inhibitors such as e.g., ipilimumab; tremelimumab; and/or nivolumab (e.g., OPDIVO™).

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises: a treatment or amelioration for a neuroendocrine tumor or a carcinoid or a side effect caused by the carcinoid or neuroendocrine tumor; for example, a drug that is an analog of somatostatin such as e.g., the peptide H-D-2Nal-Cys(1)-Tyr-D-Trp-Lys-Val-Cys(1)-Thr-NH2, or lanreotide or lanreotide acetate or lanreotide SR (e.g., SOMATULINE™), manufactured e.g., by Ipsen (Paris, France); or, octreotide (e.g., SANDOSTATIN™) or octreotide acetate LAR (SANDOSTATIN LAR™, Novartis Pharma AG).

In one exemplary method, therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein (e.g., the exemplary VT-11CR) are used with protein-bound paclitaxel and gemcitabine for the treatment of a metastatic pancreatic cancer.

In alternative embodiments, before administration of therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein, patients are provided a run-in period to stabilize patients with substantial and pre-emptive supportive care, and then to continue substantial and pre-emptive supportive care after treatment for e.g., dysfunctional cell conditions or cancers (e.g., with therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein).

In alternative embodiments, pre-emptive support care comprises use of anti-thrombic therapy, stents (e.g., when at risk of obstruction), and drugs such as granulocyte-colony stimulating factor (G-CSF or GCSF, also known as colony-stimulating factor 3, or CSF 3); and others are used in response to deficiencies and/or for symptoms as they arise.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprises, or the cancer drug or a cancer adjunctive or support therapy comprises, or the pre-emptive support care or post-treatment support care comprises:

- Prophylactic use of anti-thrombic therapy; e.g., either low molecular weight heparin ("LMWH") and/or direct factor Xa inhibitors, such as e.g., rivaroxaban (e.g., XARELTO™), apixaban (e.g., ELIQUIS™), dabigatran etexilate (e.g., PRADAXA™);
- Prophylactic use of GCSF (e.g., immediately after chemo to prevent neutropenia);
- Use of Vitamin D, e.g., administered as an injection;
- Use of Pancreatic enzymes replacement therapy to address enzyme deficiencies (which can be associated with pancreas exocrine organ failure);
- Diabetes management (e.g., metformin, GLUCOPHAGE™, insulin, and/or LANTUS™), often associated with pancreas cancer due to pancreas endocrine organ failure/type 3 diabetes, and/ or general diabetes control;
- Biliary stents (e.g., metal coated), are very commonly given when pancreatic cancer is ductal in nature;

- H2 antagonists for GI bleeding (e.g., famotidine, PEPCID™), this can synergize with administrations of an exemplary drug combination as provided herein, e.g., VT-11CR;
- Adequate pain control with opioids;
- Use of melatonin at night for sleep, this can synergize with exemplary drug combination as provided herein, e.g., VT-11CR;
- Pain control with opioids; or
- Any combination thereof.

In alternative embodiments, the therapeutic combinations, pharmaceutical compositions, formulations and kits as provided herein further comprise, or the cancer drug or a cancer adjunctive or support therapy comprises (or comprises use of):

- a Lymphocyte-Activation Gene (LAG) or a Lymphocyte-Activation Gene 3 ("LAG-3") (or immune checkpoint LAG-3) modulator, wherein optionally the LAG or LAG-3 modulator (or immune checkpoint molecule) comprises:
  - Eftilagimod Alpha (or LAG-3Ig or IMP 321) (Prima BioMed Ltd, Australia)
  - LAG525 (Novartis), optionally in combination with PDR001, an anti-PD-1 monoclonal antibody,
  - Relatlimab (or BMS-986016) (Bristol-Myers Squibb), a LAG inhibitor,
  - GSK2831781 (GlaxoSmithKline (GSK)), a monoclonal antibody that targets LAG,
  - BI754111 (Boehringer Ingelheim), a monoclonal antibody that targets LAG-3,
  - MGD013 (MacroGenics), an IgG4κ bispecific antibody that binds PD-1 and LAG-3 concomitantly or independently,
  - MK4280 (Merck Sharp & Dohme Corp.), optionally in combination with pembrolizumab,
  - REGN3767 (Regeneron Pharmaceuticals), optionally with REGN2810 (Anti-PD1), and/or
  - TSR-033 (Tesaro, Inc.), an anti-LAG-3 Monoclonal Antibody, optionally in combination with an anti-PD-1 molecule or antibody;
- an IL-10, optionally a recombinant IL-10, optionally pegilodecakin (or AM0010) (ARMO BioSciences) (an IL-10 linked to polyethylene glycol (PEG), or PEG-IL-10), and optionally in combination with folinic acid, 5-fluorouracil, and/or oxaliplatin;

- an IL-2 or analog thereof, optionally an IL-2 receptor agonist, or an interferon (IFN), and optionally the interferon is an alpha-IFN or a gamma-IFN; and optionally the IL-2 or analog thereof or IL-2 receptor agonist is a recombinant IL-2, an aldesleukin or a PROLEUKIN® (made by genetically engineered E. coli strain containing an analog of the human interleukin-2 gene) (Prometheus Laboratories), wherein optionally the IL-2, recombinant IL-2, or aldesleukin is dosages at about: 1 to 20, 2 to 10, 4 to 5, or 4.5 millions of IUs per cycle; or is dosaged for: 1 to 5, 2 to 4, or 3 cycles number of cycles of therapy, and optionally the IL-2 or analog thereof or IL-2 receptor agonist is NKTR-214 (Nectar), a CD122-biased agonist designed to stimulate the patient's own immune system;

- an IL-15 or analog thereof, optionally NKTR-222 (Nektar);

- a T-cell immunoglobulin and mucin-domain containing-3 ("TIM-3") antagonist, optionally belizatinib or TSR-011 (an orally available inhibitor of both the receptor tyrosine kinase anaplastic lymphoma kinase (ALK) and the tropomyosin-related kinases (TRK) TRKA, TRKB, and TRKC), or MBG453 (Novartis) an anti-TIM-3 antibody (Tim-3 is an immune checkpoint, or protein that ensures that the immune system does not mistakenly attack healthy cells; and/or

- an oncolytic virus, optionally a genetically oncolytic virus, for example:

  - a genetically engineered herpes virus, optionally talimogene laherparepvec, or T-VEC™, or IMLYGIC™, or ONCOVEX™, or RP1, RP2 or RP3 (Replimune);
  - a genetically engineered adenovirus, or enadenotucirev;
  - a genetically engineered vaccinia virus, optionally PEXA-VEC™; or
  - a genetically engineered retrovirus, or vocimagene amiretrorepvec (Tocagen) (optionally with TOCA FC™ (extended-release 5-fluorocytosine);

- autologous Formalin-Fixed Tumor Vaccines, Cell-Lysate Tumor Vaccines;

- agonists or activators of or ligands of pattern recognition receptors (PRRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), C-type lectin receptors (CLRs), cytosolic sdDNA sensors (CDSs) and/or Toll-like receptors (TLRs); and/or any combination thereof.

Methods of administration

In alternative embodiments, provided herein are therapeutic combinations of drugs, pharmaceutical compositions, preparations and kits, that can be administered by

several routes, for formulated for administration by any of several routes, including intravenous, topical and oral, or combinations thereof.

For example, one embodiment comprises a product of manufacture comprising a pharmaceutical composition or a formulation, a blister package, a lidded blister or a blister card or packet, a clamshell, a tray or a shrink wrap, or a kit, comprising: therapeutic combinations of drugs, pharmaceutical compositions or preparations as provided herein for oral administration.

In alternative embodiments, although all ingredients can be in one blister package, a lidded blister or a blister card or packet, a clamshell, a tray or a shrink wrap, or a kit, separate ingredients can be formulated e.g., for topical application, for oral or for topical application. Each ingredient can be either separately packaged, or can be formulated as one unit dose, e.g., as one tube (e.g., with gel, lotion etc.), ampoule, blister packette and the like.

Packaging and Drug Delivery Systems

In alternative embodiments, provided are therapeutic combinations, preparations, formulations and/or kits, comprising combinations of ingredients, as described herein. In one aspect, each member of the combination of ingredients is manufactured in a separate package, kit or container; or, all or a subset of the combinations of ingredients are manufactured in a separate package or container. In alternative aspects, the package, kit or container comprises a blister package, a clamshell, a tray, a shrink wrap and the like.

In one aspect, the package, kit or container comprises a “blister package” (also called a blister pack, or bubble pack). In alternative embodiments, provided are therapeutic combinations, preparations, formulations and/or kits manufactured as “blister packages” or as a plurality of packettes, including as lidded blister packages, lidded blister or blister card or packets or packettes, or a shrink wrap.

In one aspect, the blister package is made up of two separate elements: a transparent or occlusive plastic cavity shaped to the product and its blister foil backing. These two elements are then sealed together into a blister strip of one or more blister with each blister an environmentally (e.g. moisture, pathogen, light) protected unit dose. One or more blister strips can be further joined with board material which allows the product to be package, handled, hung, displayed or shipped without damaging the blister seal and provided child resistant features. Exemplary types of “blister packages” include: Face

seal blister packages, gang run blister packages, mock blister packages, interactive blister packages, slide blister packages.

Blister packs, clamshells or trays are forms of packaging used for goods; thus, provided are blister packs, clamshells or trays comprising a composition (e.g., a (the multi-ingredient combination of drugs as provided herein) combination of active ingredients) as provided herein. Blister packs, clamshells or trays can be designed to be non-reclosable, so consumers can tell if a package has already opened. They are used to package for sale goods where product tampering is a consideration, such as the pharmaceuticals as provided herein. In one aspect, a blister pack as provided herein comprises a molded PVC base, with raised areas (the "blisters") to contain the tablets, pills, etc. comprising the combinations as provided herein, covered by a foil laminate. Tablets, pills, etc. are removed from the pack either by peeling the foil back or by pushing the blister to force the tablet to break the foil. In one aspect, a specialized form of a blister pack is a strip pack. In one aspect, in the United Kingdom, blister packs adhere to British Standard 8404.

In alternative embodiments, laminated aluminum foil blister packs are used, e.g., for the preparation of drugs designed to dissolve immediately in the mouth of a patient. This exemplary process comprises having the drug combinations as provided herein prepared as an aqueous solution(s) which are dispensed (e.g., by measured dose) into an aluminum (e.g., alufoil) laminated tray portion of a blister pack. This tray is then freeze-dried to form tablets which take the shape of the blister pockets. The alufoil laminate of both the tray and lid fully protects any highly hygroscopic and/or sensitive individual doses. In one aspect, the pack incorporates a child-proof peel open security laminate. In one aspect, the system gives tablets an identification mark by embossing a design into the alufoil pocket that is taken up by the tablets when they change from aqueous to solid state. In one aspect, individual 'push-through' blister packs/ packettes are used, e.g., using hard temper aluminum (e.g., alufoil) lidding material. In one aspect, hermetically-sealed high barrier aluminum (e.g., alufoil) laminates are used. In one aspect, any products of manufacture as provided herein, including kits or blister packs, use foil laminations and strip packs, stick packs, sachets and pouches, peelable and non-peelable laminations combining foil, paper, and film for high barrier packaging.

In alternative embodiments, any products of manufacture as provided herein, including kits or blister packs, include memory aids to help remind patients when and

how to take the drug. This safeguards the drug's efficacy by protecting each pill until it's taken; gives the product or kit portability, makes it easy to take a dose anytime or anywhere.

MultiRex™: Universal Oral Anti-Cancer Drug Delivery System

In alternative embodiments, provided is a universal oral anti-cancer drug delivery system comprising use of pharmaceutical dosage forms, drug delivery devices and products of manufacture as provided herein. In alternative embodiments, the universal oral anti-drug delivery system addresses the significant challenges posed when using complex oral anti-cancer therapies, including: the challenges to the prescriber to accurately prescribe, titrate and modify dosing; and e.g., for the pharmacists to fill the prescription; for the physician, oncology nurse and/or pharmacist to train and manage the patient/primary care adherence to therapy and to address side effects that may arise with use of the drug.

Complex oral therapy regimens are defined as two or more anti-cancer drugs, prescribed three-or more times per day at different amounts between AM and PM and may also be prescribed at different dosage amounts by day of week and week of a cycle of anti-cancer therapy. A cycle of anti-cancer therapy ranges from one to twelve weeks with most from two to six and most common four weeks or one-month. A complex regimen also is one prescribed at different dose strengths and requiring dose modifications in response to side-effects of therapy or changes in health status of the patient.

In alternative embodiments, oral anti-cancer drug delivery systems provided herein as provided herein, e.g., MULTIREX™, addresses the problems of compliance for complex oral therapy regimens. For example, studies show that for just single oral cancer which are prescribed three or more times per day, only 25% to 50% of patients are able to adhere 80% or more to time-interval administration within two hours of the indicated time. Studies show that adherence rates decline further with use of multi-oral agents, that vary over course of a treatment cycle and in in elderly, symptomatic, single patients and/or with other risk factors of poor adherence. Alternative embodiments of universal multi-drug delivery system are designed address these problems.

Alternative embodiments of oral anti-cancer drug delivery systems provided herein as provided herein, e.g., MULTIREX™, overcome the challenges of complex oral

anti-cancer therapies by preserving the pharmacokinetic/pharmacodynamic (PK/PD) profile of a complex regimen of any complex oral therapy, and translate the regimen into a single fixed dose combination drug product that can be accurately prescribed by the oncologist and adhered to by the patient.

In alternative embodiments, the universal multi-drug delivery systems provided herein comprise, e.g., Level 1 VT-11CR AM and/or Level 2 VT-11CR AM, and, VT-11CR PM; for example, the universal multi-drug delivery systems as provided herein can comprise:

1. Immediate release (IR) (e.g., etodolac) and delayed (or controlled) release (DR) active agents, e.g., propranolol, can achieve a pulsatile release (optionally of between about 40% to 95% of the drug) in 3 to 7 hours, and recapitulate (or approximately reproduce) using a once a day or a twice a day (BID) administrative protocol the PK/PD profile of a three times a day (TID), four times a day (QID) or more dosing of the agents;
2. Combination morning (or AM) capsule, tablet, pill or the like, comprised of one or more active agents in an IR and/or DR release forms, and a PM (evening or bedtime) capsule, tablet, pill or the like, comprised of one or more active agents with IR and/or DR release profile. The capsules, tablets, pills or the like, are placed on a blister card or equivalent providing multi-day, e.g., a seven day, supply with/without a spare dose;
3. The composition of the AM and PM capsules, tablets, pills or the like may vary by day of week and week within cycle of therapy;
4. The capsules, tablets, pills or the like are contained in unit dose blister card or equivalent with foil backing that requires minimal finger strength to remove the capsules, tablets, pills or the like;
5. The blister card or equivalent is in a child resistant enclosure system that is elderly friendly and requires minimal grip strength to release the blister card or equivalent;
6. On the outside of the enclosure system, a telephone number for 24/7 healthcare professional support and/or a QR code (abbreviated from Quick Response Code, is the trademark for a type of matrix barcode or two-dimensional barcode) for 24/7 mobile phone access to patient support material and a healthcare professional;

7. The blister card or equivalent will function as a physical data capture device for use by the patient and/or primary care as a reminder system to improve adherence and avoid both missed dosing as well as double dosing;
8. The blister card or equivalent will also function as physical data capture device for use by the healthcare professional to monitor adherence on daily, weekly or cycle basis, identify lack of adherence by time of day/day of week/week in cycle and then through dialogue with the patients and/or caregiver; and to identify barriers to adherence, propose interventions to overcome barriers to adherence and then monitor interventions to assure adherence;
9. A medical electronic monitory system that records administration time and transmits information to near-field communication (NFC) enabled mobile phone;
10. A database system that captures data from by manual or automated loading of compliance data; the database system is linked to pharmacy and other healthcare information systems; the database can track and compare adherence rates by healthcare professional, by site and by payer;
11. A health care provider (HCP) and a site adherence rate data will enable continuous improvement in adherence via identification of:
    a. Underperformers that will enable HCP and site-specific interventions, including in service training programs, and/or
    b. Overperformers that will enable HCP and site-specific discovery and dissemination of best practices across; and/or
12. A payer adherence rate data will support outcomes based reimbursement.

In alternative embodiments, universal multi-drug delivery systems as provided herein, e.g., MULTIREX™, and pharmaceutical dosage forms, drug delivery devices and products of manufacture as provided herein comprise use of non-steroidal anti-inflammatory drugs (NSAIDs) and Beta Blockers (or beta-adrenergic blocking agents; these are competitive antagonists that block the receptor sites for the endogenous catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) on adrenergic beta receptors, of the sympathetic nervous system), e.g., propranolol (which blocks the action of epinephrine (adrenaline) and norepinephrine (noradrenaline) at both β_1- and β_2-adrenergic receptors) and etodolac (blocks or inhibits cyclooxygenase, or "COX", and therefore is called a "coxib"), which over the last thirty years have shown

significant efficacy in animal models of cancer. These agents' mode of action (MOA) are multifactorial, however, in models of metastatic cancer, the agents, individually and synergistically, can switch M2 Macrophages into M1 state and thereby attract and activate NK cells and T-cells to kill cancers cells.

However, these positive animal study results have not translated in to clinical success. All phase 3 studies of NSAIDs, including COX-2 selective inhibitors such as celecoxib for treatment of metastatic cancer have failed to show significant efficacy. Additionally, a meta-analysis (a statistical analysis that combines the results of multiple scientific studies) of all retrospective studies of cancer patients using beta blockers shows no correlation with patient survival. Animal studies suggest the failure of these studies is due to use in non-responsive population (M2 Macrophage Low cancer types, among other non-responding populations); the use of high and continuous dosing of each agent that leads to reduced loss of efficacy, tachyphylaxis and increased toxicity and the use of specific agents within each class that lack sufficient activity in relevant tissue compartments or have off-target effects that offset the efficacy and induce dose limiting toxicities.

However, a pilot study of propranolol and etodolac ("PE") and protein-bound paclitaxel (albumin-bound paclitaxel, or nab-paclitaxel, or ABRAXANE®) and gemcitabine (GEMZAR®), or "GemNab", for pancreas cancer (metastatic pancreatic cancer) showed significant efficacy, as is further discussed in Example 2, below. Based on animal data, the success is consistent with low, intermittent and combination use of each agent in a highly responsive population of patients. This specific regimen and study design had significant challenges that limit its translation into a multi-center study or a community setting because, for example:

i. The pilot study treated only patients that had high CRP/Albumin ratio (a >0.18) a markers of systemic inflammation that is highly correlated with M2 macrophage high cancers (e.g. likely responders). Patients in a community setting are comprised of both M2 macrophage high and low patients (e.g. likely responder and non-responders);

ii. The pilot study incorporated a two-week work-up period where patients received extensive and pre-emptive support care and assessments to assure only stable patients were randomized into the study and adequate primary care-giver support was present to aid the patient; however, in a realistic community setting, both

stable and unstable patients are treated and patients with extensive and limited primary caregiver support are treated;

iii. Because the patients were stable and carefully observed by a highly trained investigator, the investigator was able to titrate, separately, propranolol and etodolac, based on changes in heart rate, liver function, pain, among other responses of each patient during a one-week titration period to five different dose combination of propranolol and etodolac administrated three times per day; in a community setting, titration of etodolac and propranolol, separately is not possible given the limited time to observe the patient, the frequent treatment of unstable/symptomatic patients and the lack of specialized investigator training of the oncologists;

iv. Because of attention of the practice on the conduct of the clinical study and the extensive primary care-giver support available at the homes of the patients, the patients were able to adhere to individually optimized, two drugs, multiple doses at three times per day regimen; while in a community setting, less than 50% of cancer patients were able adhere to mono-therapy, single dose, anti-cancer therapy within the recommended time interval (+/- three hours).

Thus, to translate the PE (Propranolol-Etodolac)+Gem-nab pilot study results into a community setting, an effective therapy needs e.g., to use a robust biomarker to identify M2 macrophage high patients; to simplify dosing for easy titration and dose modification; and/or to improve drug deliver and packaging to improve adherence, which problems are significantly addressed by the specific dose amounts and dose release profile of propranolol/ etodolac (PE) as provided herein, and the universal multi-drug delivery systems provided herein, e.g., MULTIREX™, and the pharmaceutical dosage forms, drug delivery devices and products of manufacture as provided herein.

In alternative embodiments, a robust biomarker is used to identify M2 macrophage high patients and for selecting an individual (e.g., patient) in need of treatment using a therapeutic combination as provided herein comprises: a lymphocyte-to-monocyte ratio (LMR) of less than 6 or less than 5 or less than 4 or less than 3 is used as selection for patients. LMR is a surrogate marker for M2 Macrophage Tumors, and is available (able to be calculated by) using standard complete blood cell count tests. Other markers for selecting an individual (e.g., patient) in need of treatment using a therapeutic

combination as provided herein include: C-reactive protein (CRP)/Albumin of greater than 0.05 or greater than 0.8 or greater than 0.10 or greater than 0.12 or greater than 0.15 or greater 0.18, and neutrophil-to-lymphocyte ratio (NLR) of greater than 2.0 or greater than 3.0 or greater than 4.0 or greater than 5.0. These other markers are correlated with LMR and M2 macrophage high tumors.

In alternative embodiments, simplify dosing for easy titration and dose modification and the use of the universal multi-drug delivery systems provided herein, and the pharmaceutical dosage forms, drug delivery devices and products of manufacture as provided herein. For example, to determine optimal dosaging, data from four randomized controlled trials (RCTs) was applied to a modified 3+3 dose finding algorithm (see e.g., Braun, et al., Clin. Trials 2011 Jun; 8(3):247-59) determined an optimal high dose of 64 mg propranolol with 32 mg AM, 32 mg afternoon, and 680 mg etodolac, with 140 mg AM and 540 mg administered in the PM.

In alternative embodiments, use of the universal multi-drug delivery systems provided herein, e.g., MULTIREX™, and the pharmaceutical dosage forms, drug delivery devices and products of manufacture as provided herein, are drug delivery systems that can improve adherence to optimized dosage amounts and timing by converting from QID or TID to a BID dosage regimen by using delayed (DR) (or controlled) "pulsatile" release beads or tablets or equivalents, e.g., using Dose Level 1 VT-11CR AM or Dose Level 2 VT-11CR AM, as provided herein. Use of a delayed "pulsatile" release regimen eliminates the need for difficult to adhere to time-interval dosing, and retains intermittent release of drug to minimize risk of tachyphylaxis.

In alternative embodiments, the delayed "pulsatile" release regimen provided herein combines the desired drug combination, e.g., propranolol and etodolac (PE), into one single AM and one PM pill to reduce pill burden and improve adherence.

In alternative embodiments, universal multi-drug delivery systems provided herein, e.g., MULTIREX™, and pharmaceutical dosage forms, drug delivery devices and products of manufacture as provided herein, use child resistant and elderly friendly packaging, e.g., packaging compliant to U.S. Government child resistant packaging regulation that requires minimal finger and grip strength. For example, in alternative embodiments foil-only containment of pills is used.

In alternative embodiments, universal multi-drug delivery systems provided herein, e.g., MULTIREX™, and pharmaceutical dosage forms, drug delivery devices and

products of manufacture as provided herein, place AM and PM tablets, capsules, pills or equivalents on a blister card or equivalent to track usage. By tracking usage, the blister card monitor can remind the patient and/or the primary care-giver to take medication (or that medication has been taken) in AM and PM; and can facilitate discussion with health care professionals to identify and overcome barriers to adherence.

In alternative embodiments, patient usage is monitored by use of customized blister cards or equivalents using an Electronic Compliance Monitor (ECM) system (Intelligent Devices SEZC Inc. (IDI), Grand Cayman, Cayman Islands), or equivalents. For example, in alternative embodiments, the blister cards or equivalents comprise an electronic component that detects, records, safeguards and/or transmits medication removal from the blister cards or equivalents. For example, a sensor detects medication removal from the blister cards or equivalents, and this information can be transferred to a remote location for review by e.g., the drug provider and/or the primary care institution or individuals. The data transfer can be by hard contact downloading of data to a transmitting and/or storage device, and can be scanned and data downloaded remotely using a radio-frequency identification (RFID) chip, tag or device or equivalent, which can be operatively connected to a computer and/or a mobile phone or other device. Radio-frequency identification uses electromagnetic fields to automatically identify and track tags attached to objects, where the tags contain electronically stored information, which in this embodiment is transmitting whether and/or when medication is removed from each compartment of the blister cards or equivalents, or by Near-Field Communication (NFC) to a NFC-enabled mobile device or mobile phone. The NFC is a set of communication protocols that enable two electronic devices, one of which is usually a portable device such as a smartphone, to establish communication by bringing them within 4 cm (1.6 in) of each other.

In alternative embodiments, universal multi-drug delivery systems provided herein, e.g., MULTIREX™, comprises use of a box to house or enclose drug delivery devices or packages, blister packages, clamshells or trays, as provided herein, as illustrated in FIG. 19, where in this exemplary delivery system a week of pharmaceutical dosage form (e.g., one, two or three or more tablets, pills, capsules, geltabs or equivalents) are stored on four rows, two rows for administration (for opening and self-administering by user, e.g., patient) are for morning or breakfast, or AM administration, and two rows are for evening, dinnertime or PM administration; morning or breakfast, or

AM administration rows are clearly separated from the evening, dinnertime or PM administration rows, and each day, and the spare dose, are arranged in column form. In alternative embodiments the blister packages, clamshells or trays are physical linked to a storage box, wherein the blister packages, clamshells or trays slide into and out of the storage box, and in alternative embodiments if needed the PM set of rows can be folded over the AM set of rows for reinsertion of the blister packages, clamshells or trays into the storage box. In alternative embodiments, the storage box comprises sensors to detect medication removal from each of the compartments (e.g., which compartment is opened and when), and this information can be transferred to a remote location, e.g., by Near-Field Communication (NFC) to a NFC-enabled mobile device or mobile phone, for review by e.g., the drug provider and/or the primary care institution or individuals.

The invention will be further described with reference to the examples described herein; however, it is to be understood that the invention is not limited to such examples.

EXAMPLES

Example 1: Container Closure System for VT-11CR Capsules

This example demonstrates an exemplary formulation and packaging delivery system as provided herein.

Primary Container Closure System

In alternative embodiments, exemplary formulations or drug combinations as provided herein, including VT-11CR capsules, and etodolac capsules, are packaged into 8-count thermoformed polyvinyl chloride (PVC) blisters with foil-lined paper push-through lidding. Both the blister and lidding are constructed of materials that provide a barrier to oxygen and moisture. All products utilize the same packaging components. A description of the PVC blister material and push-through lidding is provided below:

- Blister material:

Description: 130 mm PVC / APPEEL® (sealing layer) / ACLAR® (moisture barrier)
Manufacturer: Amcor Flexibles (Asheville, NC • USA)

- Push-through lidding material:

Description: 130 mm Paper (bleached Kraft, 15 lb/ream) / adhesive / Foil (moisture barrier) / Heat Seal 4506

Manufacturer: Amcor Flexibles (Shelbyville, KY • USA)

Secondary Packaging

In alternative embodiments, cards are assembled in a child resistant and elderly friendly box enclosure system that requires minimal finger and grip strength to release card from box and capsules from blister.

In alternative embodiments, cards are assembled for low dose (e.g., designated "Level 1") and high dose (e.g., designated "Level 2") as described below, using 8-capsule blister strips of etodolac and 8-capsule blister strips of VT-11CR:

- Low dose ("Level 1") cards comprise one morning (AM) blister strip containing 8 VT-11CR capsules and one evening (PM) blister strip containing 8 etodolac capsules.
- High dose ("Level 2") cards comprise two morning (AM) blister strips containing a total of 16 VT-11CR capsules and two evening (PM) blister strips containing a total of 16 etodolac capsules.

This exemplary embodiment also applies to the placebo presentation (VT-11CR placebo capsules + etodolac placebo capsules).

Example 2: Exemplary Protocol Using VT-11CR Capsules

This example demonstrates an exemplary therapeutic protocol using the exemplary VT-11CR formulation and packaging delivery system as provided herein with protein-bound paclitaxel (albumin-bound paclitaxel, or nab-paclitaxel, or ABRAXANE®) and gemcitabine (GEMZAR®), or "GemNab", for metastatic pancreatic cancer.

Patients take their morning dose in the morning within one hour after breakfast (target between 8:00 AM and 10:00 AM). The evening dose should be taken within one hour after the evening meal (target 7:00 PM to 10:00 PM), approximately 12 hours after the morning dose. Patients should consume food prior to taking the VT-11CR medication. In the evening, a small snack should be sufficient pre-dose but the VT-11CR medication should be taken right after eating. A mid-day meal or snack is also recommended.

VT-11CR study medication can continue until intolerable adverse events, patient refusal to continue treatment or withdrawal of consent for the study, PD or the patient starts a new anti-cancer treatment.

If GemNab has been discontinued and the patient's disease has not yet progressed, treatment with VT-11CR study medication can continue per the Investigator's discretion until the patient starts a new anti-cancer treatment. The patient will undergo an End-of-Treatment visit when the VT-11CR study medication has been discontinued.

Standard of care chemotherapy will consist of protein-bound paclitaxel 125 mg/m2 given intravenously Days 1, 8 and 15 of a 28-day cycle) and gemcitabine 1,000 mg/m2 (given intravenously Days 1, 8 and 15 of a 28-day cycle).

GemNab can continue until intolerable adverse events, patient refusal to continue treatment or withdrawal of consent for the study, PD or the patient starts a new anti-cancer treatment. If treatment with one of the components of GemNab is discontinued (e.g. for toxicity reasons), the other component should also be discontinued.

If VT-11CR study medication has been discontinued and the patient's disease has not yet progressed, treatment with GemNab can continue per the Investigator's discretion. The patient will undergo an End-of-Treatment visit when the VT-11CR study medication has been discontinued.

Pharmacokinetics (PK) parameters for assessment can include maximum concentration (Cmax), time to reach maximum concentration (tmax), half-life ($t_{1/2}$), area under the curve (AUC)0-12, AUC0-t, total clearance after oral administration (CL/F), apparent volume of distribution after non-intravenous administration (Vd/F), and terminal disposition rate constant (λz). Other PK parameters may be calculated, as appropriate.

All patients received standard of care GemNab, as well as prophylactic granulocyte colony-stimulating factor (CSF), low-molecular weight heparin, opioids for pain and other supportive care as needed. Upon PD or intolerable adverse effects, patients discontinued GemNab and were provided supportive care only; no second-line therapy was provided.

In an earlier study, as illustrated in FIG. 4, patients were assigned to the propranolol and etodolac treatment arm received a 1-week run-in period of 40 mg of propranolol (20 mg in the AM and 20 mg in the afternoon) and 600 mg of etodolac in the PM. If tolerated, the propranolol dose was then titrated upwards to 40 mg in the AM and 40 mg in the afternoon to achieve a resting heart rate of 60 beats/minute. For patients experiencing morning pain, 200 mg of etodolac was added in the AM. For patients experiencing gastric discomfort, etodolac was reduced to 400 mg in the PM. Patients in the treatment arm could continue propranolol and etodolac post-disease progression if the

investigator-deemed patient was receiving a clinical benefit. Patients were followed until death.

This earlier study enrolled 37 patients. The co-administration of propranolol and etodolac (PE) plus GemNab was associated with an 8.3-month increased median OS in patients with locally advanced or metastatic pancreatic cancer compared to patients treated with GemNab alone (9.1 vs. 17.4 months; HR 0.096; $p < 0.001$); see FIG. 5 (shows overall survival of GemNab ± propranolol and etodolac in patients with locally advanced / metastatic pancreatic cancer). It is notable that these were highly-selected patients with substantial supportive and pre-emptive care. Patient baseline characteristics are shown in Table 2, below. All patients in the study showed markers of systemic inflammation (CRP/albumin ratio > 0.18). No propranolol- or etodolac-associated serious adverse events (SAEs) were reported in the study.

Table 2 Baseline characteristics in patients treated with GemNab ± propranolol and etodolac

Characteristic	Propranolol + Etodolac + GemNab (n = 20)	GemNab (n = 17)
Male %	70	59
Mean age, years	61.7	60.0
Disease Stage, %		
Locally advanced	35	24
Metastatic	65	76

Characteristic	Propranolol + Etodolac + GemNab (n = 20)	GemNab (n = 17)
Mean ECOG Score	1.9	2.1
Symptoms present, %		
Pain	90	88
Weight loss	65	47
Jaundice	30	65
Vomiting	33	24

ECOG Eastern Cooperative Oncology Group.

For the VT-11CR study, as summarized in FIGs. 3-5, a randomized, double-blind, placebo-controlled two-staged study in which patients is randomized on a 1:1 basis to receive the standard of care GemNab, with VT-11CR study medication consisting of either VT-11CR (Treatment Arm 1) or placebo (Treatment Arm 2). Patients will have previously untreated, metastatic pancreatic cancer with documented measurable disease according to RECIST 1.1.

After confirmation of eligibility and randomization, patients initiate VT-11CR study medication at Dose Level 1 on study Day –7. Upon completing of at least two days of treatment and in the absence of any related ≥ Grade 2 adverse events, treatment with VT-11CR study medication at Dose Level 2. Upon completing at least 3 hours of treatment and in the absence of any related ≥ Grade 2 adverse events, GemNab will start on study Day 1. VT-11CR study medication and GemNab can continue until intolerable adverse events, patient refusal to continue treatment or withdrawal of consent for the study, PD or the patient starts a new anti-cancer treatment. If GemNab has been discontinued and the patient's disease has not yet progressed, treatment with VT-11CR study medication can continue per the Investigator's discretion until the patient starts a new anti-cancer treatment. Similarly, if VT-11CR study medication has been discontinued and the patient's disease has not yet progressed, treatment with GemNab can continue per the Investigator's discretion. The patient will undergo an End-of-Treatment visit when the VT-11CR study medication has been discontinued.

Example 3: Stability and Dissolution Profiles of Exemplary VT-11CR Capsules

This example describes stability and dissolution profiles of the exemplary VT-11CR capsules as provided herein.

Stability of propranolol capsules containing immediate release (16 mg) and delayed release (or controlled release) (DR) (16 mg) formulations of active moiety, conducted at 5°C / ambient RH (relative humidity).

Stability of combination capsules containing propranolol immediate release (16 mg) and delayed release (or controlled release) (DR) (16 mg) formulations of active moiety with etodolac (70 mg), conducted at 5°C / ambient RH.

The individual and combination products that were tested are defined as follows:

Individual Product - Propranolol (32 mg active) is tested as a single gelatin capsule containing a formulation of polysaccharide microbeads coated with propranolol

(16 mg of the active moiety for immediate release (IR)) and a formulation of polysaccharide microbeads or microparticles coated with propranolol and EUDRAGIT® polymer to modulate the release rate (16 mg of the active moiety for delayed release (DR)).

Combination Product – The combination product is tested as a single gelatin capsule containing propranolol (32 mg active) in the same two formulations described above (16 mg IR + 16 mg DR) with etodolac (70 mg active).

The dissolution profiles of propranolol (individual product) at 5°C / ambient RH, 25°C / 60% RH, 30 °C / 65% RH and 40°C /75% RH are shown in FIGs. 8 to 11, respectively. The long-term storage condition was initially assigned as refrigerated (2 to 8°C). Based on this assignment, the other stability storage temperatures/humidities represent accelerated conditions that may be used to provide an extrapolated shelf life at the long-term storage condition or to support high-temperature excursions from the long-term storage condition (such as those that may occur during shipment or day-to-day patient use). In FIGs. 8 to 11, error bars utilize ±%RSD; also, for clarity, the 24-hour dissolution time point is not provided in the graphical presentation, as complete dissolution was consistently achieved by 12 hours.

Assignment of an Initial Dissolution Specification for Propranolol

Based on the stability data generated to date, a dissolution specification may be proposed for propranolol (individual product).

Proposed Propranolol Individual Product (16 mg IR + 16 mg DR) Dissolution Acceptance Criteria:

Meets S1, S2 or S3 at each time point, according to the criteria specified below:

1 hour: 45% - 55% dissolved

5 hours: 60% - 80% dissolved

12 hours: ≥ 90% dissolved

Dissolution testing is continued through the three levels S1, S2 and S3 unless the results conform at either S1 or S2. S1 (6 capsules tested) requirements: No individual value lies outside each of the stated ranges, and no individual value is less than the stated amount at the final time point. S2 (6 capsules tested) requirements: The average value of the 12 units (S1 + S2) lies within each of the stated ranges and is not less

than the stated amount at the final time point. None is more than 10% of labeled content outside each of the stated ranges. None is more than 10% of labeled content below the stated amount at the final time point. S3 (12 capsules tested) requirements: The average value of the 24 units (S1 + S2 + S3) lies within each of the stated ranges and is not less than the stated amount at the final time point. Not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges. Not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final time point. None of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final time point.

The 5°C dissolution profiles are sufficiently consistent across all stability time points and satisfy the three critical parameters for the mixture of IR and DR propranolol formulations contained in the gelatin capsule: (1) the 1-hour time point verifies that the IR formulation of propranolol has fully released, and that dose dumping of propranolol from the DR formulation has not occurred, (2) the intermediate time points exhibit a consistent release rate of propranolol from the DR formulation, and (3) the final time point ensures complete propranolol release from the DR formulation. As additional batches of product are generated, acceptance criteria may be reviewed and tightened as appropriate.

Long-Term Storage Condition and Shelf Life

Based on stability data obtained to date, a nine-month shelf life has been established for propranolol individual product capsules. The long-term storage condition is refrigerated (2 to 8°C). Accelerated stability data support short-term excursions (less than or equal to 1 week) from 8°C to 25°C, such as those that may occur during shipment or day-to-day patient use. The T=0, 9-month 5°C / ambient RH and 9-month 25°C / 60% RH dissolution profiles (as illustrated in FIG. 12) all meet the proposed dissolution acceptance criteria for propranolol.

There is clear degradation of dissolution performance at temperature and humidity combinations at or above 30°C / 65% RH. Release rate appears to be hindered, and there is significant variability between vessels. Gelatin, in the presence of certain compounds and/or in certain storage conditions, including but not restricted to high humidity and temperature, may become cross-linked. A pellicle may form on the external and/or internal surface of the gelatin capsule shell, preventing the drug from being

released during dissolution testing. Dissolution testing of cross-linked capsules can result in slower release of the drug or no release at all. The degree of cross-linking is not necessarily uniform within one capsule or among different capsules. Consequently, there could be high variability in the dissolution results if the gelatin capsules become cross-linked. Enzymes can be added to the dissolution medium to overcome this problem.2 Alternatively, there may be a stability issue with the formulation of polysaccharide microbeads or microparticles coated with propranolol (with (DR) or without (IR) the additional EUDRAGIT™ coating). One way to assess this would be to separately encapsulate the IR and DR formulations and perform stability testing on each type of capsule, and compare to the un-encapsulated formulations stored in a sealed non-reactive container.

Graphical Representations of Dissolution Data

For the combination product, propranolol (16 mg IR + 16 mg DR) with etodolac (70 mg), we have prepared graphical representations of the dissolution data. The dissolution profiles of propranolol (solid lines) and etodolac (dashed lines) at 5 ºC / ambient RH, 25ºC / 60% RH, 30ºC / 65% RH and 40ºC / 75% RH are shown in FIGs. 13 to 16, respectively. As with the dissolution profiles of the individual product, the dissolution profiles of propranolol in combination with etodolac 70 mg are most consistent across time points under the refrigerated storage condition (5 ºC, refer to FIG. 13) and for one month at the 25 ºC / 60% RH storage condition (refer to FIG. 14). There is pronounced degradation of dissolution performance at temperature and humidity combinations at or above 30ºC / 65% RH, as well as at the 25ºC / 60% RH time points in excess of one month. Release rate of both propranolol and etodolac is significantly hindered, and there is significant variability between vessels. (refer to FIG. 14 (≥ 2 months), FIG. 15 and FIG. 16 respectively). As with the individual product, cross-linking of the gelatin capsule shell, or an excipient stability or compatibility issue, may be responsible for this observation.

Assignment of Initial Dissolution Specifications for Propranolol and Etodolac

Based on the stability data generated to date, dissolution specifications may be proposed for propranolol and etodolac (combination product).

Proposed Propranolol (16 mg IR + 16 mg DR) w/ Etodolac 70 mg Combination Product, Dissolution Acceptance Criteria: Propranolol meets S1, S2 or S3 at each time point, according to the criteria specified below:

1 hour: 45% - 55% dissolved

4 hours: 45% - 55% dissolved

6 hours: 65% - 85% dissolved

12 hours: ≥ 90% dissolved

Dissolution testing is continued through the three levels S1, S2 and S3 unless the results conform at either S1 or S2. S1 (6 capsules tested) requirements: No individual value lies outside each of the stated ranges, and no individual value is less than the stated amount at the final time point. S2 (6 capsules tested) requirements: The average value of the 12 units (S1 + S2) lies within each of the stated ranges and is not less than the stated amount at the final time point. None is more than 10% of labeled content outside each of the stated ranges. None is more than 10% of labeled content below the stated amount at the final time point. S3 (12 capsules tested) requirements: The average value of the 24 units (S1 + S2 + S3) lies within each of the stated ranges and is not less than the stated amount at the final time point. Not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges. Not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final time point. None of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final time point.

Proposed Etodolac 70 mg w/ Propranolol (16 mg IR + 16 mg DR) Combination Product, Dissolution Acceptance Criteria Etodolac meets S1, S2 or S3 according to the criteria specified below:

1 hour: ≥ 90% dissolved (Q=85%)

S1 (6 capsules tested) requirements: Each unit is ≥ 90% dissolved (≥ Q + 5%).

S2 (6 capsules tested) requirements: The average value of the 12 units (S1 + S2) is ≥ 85% (≥ Q), and no unit is < 70% (< Q – 15%).

S3 (12 capsules tested) requirements: The average value of the 24 units (S1 + S2 + S3) is ≥ 85% (≥ Q). Not more than 2 of the 24 units are < 70% (< Q – 15%), and no unit is < 60% (< Q – 25%).

Dissolution testing is continued through the three levels S1, S2 and S3 unless the results conform at either S1 or S2.

The 5°C dissolution profiles are sufficiently consistent across all stability time points and satisfy three critical parameters for the combination of propranolol IR/DR formulations and etodolac contained in a single gelatin capsule: (1a) the 1-hour time point for propranolol verifies that the release of propranolol from the IR formulation is complete, and that dose dumping of propranolol from the DR formulation has not occurred, (1b) the 1-hour time point for etodolac verifies immediate release of this active moiety, (2) after a 4-hour delay, the intermediate time points exhibit a consistent release rate of propranolol from the DR formulation, and (3) the final time point ensures complete propranolol release from the DR formulation. As additional batches of combination product are generated, acceptance criteria may be reviewed and tightened as appropriate.

Long-Term Storage Condition and Shelf Life

Based on dissolution stability data obtained to date, a 6-month shelf life has been established for combination capsules containing both propranolol IR/DR and etodolac. The long-term storage condition is refrigerated (2 – 8 °C). Accelerated stability data supports short-term excursions (≤ 1 week) from 8°C to 25°C, such as those that may occur during shipment or day-to-day patient use. The T=0, 6-month 5° C / ambient RH and 1-month 25 °C / 60% RH dissolution profiles (presented in FIG. 17) all meet the proposed dissolution acceptance criteria for propranolol and etodolac. There is pronounced degradation of dissolution performance at temperature and humidity combinations at or above 30 °C / 65% RH. Release rate of both propranolol and etodolac is significantly hindered, and there is significant variability between vessels.

FIG. 18 illustrates in tabular form the dissolution profile of Propranolol HCl, 16 mg IR and 16 mg DR, in combination with Etodolac 70 mg – specifically observing the 240 minutes – 360 minutes on stability up to 6 months.

A number of aspects of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other aspects are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical dosage form, a drug delivery device or a product of manufacture, comprising:

(a) a first formulation comprising or consisting of:

(i) a delayed (or controlled) release (DR) propranolol formulation and an immediate release (IR) propranolol formulation; and,

(ii) an immediate release (IR) etodolac formulation; and

(b) a second formulation comprising or consisting of an immediate release (IR) etodolac formulation,

wherein optionally the first formulation is formulated or manufactured as having the delayed (or controlled) release (DR) propranolol formulation, and/or the immediate release (IR) propranolol formulation, on or coated on the surface of or contained: in a bead, a powder, a particle, or a multilayered bead or particle,

wherein optionally the second formulation is formulated or manufactured as having the immediate release (IR) etodolac formulation, on or coated on the surface of or contained in: a bead, a powder, a particle, or a multilayered bead or particle,

and optionally the bead, powder, particle or the multilayered bead or particle is contained in a pill, a capsule, a tablet, or a geltab, or equivalents, for oral delivery,

wherein optionally the pill, capsule, tablet, geltab or equivalent for oral delivery is a hard gelatin capsule or equivalent, or comprises a hard gelatin or equivalent,

wherein:

the delayed (or controlled) release (DR) propranolol formulation comprises a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof,

the immediate release (IR) propranolol formulation comprises a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof, and

the immediate release (IR) etodolac formulation comprises a racemic R(+) and S(–) mixture of etodolac, a substantially pure (S)-enantiomer of etodolac, or a pharmaceutically acceptable salt thereof, or mixtures thereof,

and optionally the immediate release (IR) propranolol formulation comprises particles, powders, pellets, or beads (or a core comprising particles, powders, pellets, or beads), and the particles, powders, pellets, or beads are coated with or have contained therein:

a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof;

and optionally the immediate release (IR) etodolac formulation comprises particles, powders, pellets, or beads (or a core comprising particles, powders, pellets, or beads), and the particles, powders, pellets, or beads are coated with or have contained therein:

a racemic R(+) and S(–) mixture of etodolac, a substantially pure (S)-enantiomer of etodolac, or a pharmaceutically acceptable salt thereof, or mixtures thereof;

and optionally the delayed (or controlled) release (DR) propranolol formulation comprises particles, pellets, or beads (or a core comprising particles, pellets, or beads), and the particles, pellets, or beads are coated with or have contained therein:

a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof, and,

the optionally particles, powders, pellets, or beads comprise a membrane or a coating comprising a water insoluble polymer or a combination of a water insoluble polymer and a water soluble polymer,

wherein the pharmaceutical dosage form, the drug delivery device or the product of manufacture exhibits an *in vitro* dissolution profile, or an *in vivo* human dissolution profile,

wherein optionally the *in vitro* dissolution profile is determined by testing according to United States Pharmacopoeia dissolution test method USP Apparatus 1,

Baskets @ 100 rpm, Drug Release Test 1 using 900 mL of pH 1.2 buffer for 1.5 hours followed by testing in 900 mL of pH 6.8 at 4, 8, 14, and 24 hours,

and the *in vivo* human dissolution profile of propranolol is based on an oral administration to an individual in need thereof:

after 1.0 hour: not less than about 35%, 40%, 45% or 50% of the total propranolol is released (or dissolved); or, about 50% +/- 15%, of the total propranolol is released (or dissolved);

after 2 hours: about 55 +/- 15% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 4 hours: about 60 +/- 15% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 6 hours: about 80 +/- 15% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test; and,

after 8 hours: not less than about 90% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test.

2. The pharmaceutical dosage form of claim 1, wherein the dissolution profile of propranolol corresponds to the following pattern:

(a) after 1.0 hour: not less than about 50% +/- 10%, of the total propranolol is released (or dissolved);

after 2 hours: about 55 +/- 10% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 3 hours: about 60 +/- 10% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 6 hours: about 80 +/- 10% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test; and,

after 8 hours: not less than about 95% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

or

(b) after 1.0 hour: about 50% +/- 5%, of the total propranolol is released (or dissolved);

after 2 hours: about 55 +/- 5% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 3 hours: about 60 +/- 5% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test;

after 6 hours: about 80 +/- 5% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test; and,

after 8 hours: not less than about 97% of the total propranolol is released *in vivo,* or dissolved according to the United States Pharmacopoeia dissolution test.

3. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein in the first formulation, the amount of propranolol in the delayed (or controlled) release (DR) propranolol formulation and the amount of propranolol in the immediate release (IR) propranolol formulation are present in a ratio of from:

about 99:1 to 80:20 or 60:40 or 40:60,

about 95:5 to 75:25 or 65:35 or 55:45 or 45:55 or 35:65, or

about 10:90 to 30:70 or 50:50 or 70:30.

4. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein in the first formulation the immediate release (IR) propranolol formulation releases substantially all of the racemic R(+) and S(–) mixture of propranolol, and substantially all of the pure (S)-enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, contained therein during the first hour of *in vitro* dissolution testing, or during the first hour after *in vivo* oral administration.

5. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein in the first formulation and/or the second formulation the immediate release (IR) etodolac formulation substantially releases all of the racemic R(+) and S(–) mixture of etodolac, the substantially pure (S)-enantiomer of etodolac, or the pharmaceutically acceptable salt thereof, or mixtures thereof, contained therein during the first hour of *in vitro* dissolution testing, or during the first hour after *in vivo* oral administration.

6. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the water insoluble polymer comprises an ethylcellulose, a cellulose acetate, an ammonio methacrylic acid copolymer, or mixtures thereof.

7. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of claim 1, wherein said water insoluble polymer and water soluble polymer are present in a weight ratio of from about 0:100 to 60:40.

8. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein said core particles or beads comprise or are manufactured as sugar spheres, cellulose spheres, silicone dioxide spheroids, acidic buffer crystals, or alkaline buffer crystals.

9. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein said core particles or beads further comprise:

(a) a polymeric binder;

(b) a seal coating; or

(c) non-pareil seeds and a polymeric binder in the immediate release (IR) propranolol formulation or the immediate release (IR) etodolac formulation.

10. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the water soluble polymer

comprises a hydroxypropylcellulose, a hydroxypropylmethylcellulose, a methylcellulose, a polyethylene glycol, a polyvinylpyrrolidone or a mixture thereof.

11. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, configured or manufactured as a blister card or equivalent, wherein the blister card or equivalent comprises or has contained therein or packaged therein at least one day, or two, three, four, five, six or seven days, or between about one to two weeks, or 7 to 14 days, of:

(a) a first formulation for administration in the morning or breakfast (or AM, or afternoon) formulated in a single orally administrable carrier, or 2 or 3 orally administrable carriers (wherein optionally the single orally administrable carrier, or 2 or 3 orally administrable carriers comprise one, two or three or more tablets, capsules, geltabs, or pills or equivalents), and,

(b) a second formulation for administration at dinnertime or the evening (or in the PM or at bedtime) comprising an immediate release (IR) etodolac, formulated in a single orally administrable carrier, or 2 or 3 orally administrable carriers (wherein optionally the single orally administrable carrier, or 2 or 3 orally administrable carriers comprise one, two or three or more tablets, capsules, geltabs, or pills or equivalents),

and the first formulation and the second formulation are packaged in the blister card or equivalent in separate compartments (i.e., wherein the one, two or three or more orally administrable carriers of (a) and the one, two or three or more orally administrable carriers (b) are in separate compartments on the blister card),

and optionally, between about two days and one to two or three weeks, or about 8 days to 21 days, of the one, two or three or more orally administrable carriers of the first formulation, and separately the one, two or three or more orally administrable carriers of the second formulation, are packaged and configured or spaced on the blister card or equivalent in relation to each other to reflect an administration regimen wherein the one, two or three or more orally administrable carriers of the first formulation is to be taken in the AM (morning or afternoon) and the one, two or three or more orally administrable carriers of the second formulation are to be taken in at dinnertime or the evening (or in the PM or at bedtime),

wherein optionally the blister card or equivalent comprises at least a first and a second blister strip, wherein the first blister strip contains or comprises between about two days and one to two or three weeks, or about 7 or 8 to 14 days, of the one, two or three or more orally administrable carriers of the first formulation to be taken in the AM (morning or afternoon); and the second blister strip contains or comprises between about two days and one to two weeks, or about 7 to 8 days, of the one, two or three or more orally administrable carriers of the second formulation to be taken at dinnertime or in the evening (or in the PM or at bedtime),

and optionally the one, two or three or more orally administrable carriers of the second formulation comprise immediate release (IR) etodolac formulation contained in or on or coated on a plurality of particles, a powder, pellets, or beads (or contained in or on or coated on a core comprising particles, a powder, pellets, or beads), and the IR etodolac formulation comprises:

a racemic R(+) and S(–) mixture of etodolac, a substantially pure (S)-enantiomer of etodolac, or a pharmaceutically acceptable salt thereof, or mixtures thereof;

and optionally the one, two or three or more orally administrable carriers of the second formulation are arranged in a blister card or equivalent for administration at dinnertime or in the evening or at bedtime (or in the PM) and that each administrable carrier has or all the administrable carriers in total have: between about 100 and 500 mg, between about 200 and 400 mg, between about 250 and 350 mg, about 270, or about 200, 210, 220, 225, 230, 240, 250, 260, 270, 275, 280, 290, 300, 310, 320, 330, 340, 350 mg, IR etodolac, or up to three times the amount, or between about 300 mg and 1,050 mg immediate release (IR) etodolac,

and optionally the blister card or equivalent is a thermoformed polyvinyl chloride (PVC) blister card or equivalent with a push-through lidding (optionally a foil-lined paper push-through lidding, or any air-impermeable lidding), optionally comprising a sealing layer and a moisture barrier, wherein optionally the sealing layer comprises a polyethylene polymer, optionally APPEEL®, and optionally the moisture barrier comprises a poly-chloro-tri-fluoro-ethylene (PCTFE), optionally ACLAR®.

12. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, comprising a therapeutic combination comprising:

(a)

- one, two or three or more tablets, pills, geltabs, capsules or equivalents for administration in the morning or in the AM, that each tablet, pill, geltab, capsule or equivalent has, or all tablets, pills, geltabs, capsules or equivalent in a compartment in total have:

about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of immediate release (IR) propranolol, or up to triple this amount, or between about 12 and 60 mg DR propranolol;

about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of delayed (or controlled) release (DR) propranolol, or up to triple this amount, or between about 12 and 60 mg DR propranolol; and

about 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130 or 140 mg IR etodolac, or up to triple this amount, or between about 150 and 420 IR etodolac,

and optionally each of the morning or afternoon, or AM one, two or three or more tablets, pills, geltabs, capsules or equivalents has approximately equal amounts of IR and DR propranolol (optionally about 16 mg IR and about 16 mg DR propranolol for a racemic mixture, totaling 32 mg propranolol in each tablet, or about 4 to 12 mg or 6 to 10 mg IR and about 4 to 12 mg or 6 to 10 mg DR propranolol in each tablet for a substantially pure (S)-enantiomer, of propranolol),

and optionally each set of morning or AM one, two or three or more tablets, pills, geltabs, capsules or equivalents are in one blister card or equivalent compartment and the compartments are arranged in the blister card or equivalent for morning or afternoon, or AM consumption, administration or use by a user (or a patient),

wherein optionally if two morning or AM tablets, pills, geltabs, capsules or equivalents have each 32 mg propranolol in each tablet, then the two tablets in the AM compartment total a 64 mg etodolac dosage administration for the AM, and if three morning or AM tablets, pills, geltabs, capsules or equivalents have each 32

mg propranolol in each tablet, then the three tablets in the AM compartment total a 96 mg etodolac dosage administration for the AM; and

the one, two or three or more tablets, pills, geltabs, capsules or equivalents for administration in at dinnertime or in the evening (or in the PM or at bedtime) each having or in total having between about 100 and 500 mg, between about 200 and 400 mg, between about 250 and 350 mg, about 270 mg, or about 200, 210, 220, 225, 230, 240, 250, 260, 270, 275, 280, 290, 300, 310, 320, 330, 340 or 350 mg, IR etodolac, or up to triple these amounts, or between about 300 mg and 1,050 mg IR etodolac,

and optionally each set of at dinnertime or in the evening (or in the PM or at bedtime) one, two or three or more tablets, pills, geltabs, capsules or equivalents are in one blister card or equivalent compartment and the compartments are arranged in the blister card or equivalent for at dinnertime or in the evening (or in the PM or at bedtime) consumption, administration or use by a user (or a patient),

wherein optionally if the two at dinnertime or in the evening (or in the PM or at bedtime) tablets, pills, geltabs, capsules or equivalents each have 270 mg etodolac in each tablet, then the two tablets in the PM compartment total a 540 mg etodolac dosage administration for the PM, and if there are three at dinnertime or in the evening (or in the PM or at bedtime) tablets, pills, geltabs, capsules or equivalents each having 270 mg etodolac in each tablet, then the three tablets in the PM compartment total a 810 mg etodolac dosage administration for the PM; or

(b)

- one, two or three or more tablets, pills, geltabs, capsules or equivalents for administration in the morning or breakfast, or AM, that each tablet, pill, geltab, capsule or equivalent has, or all tablets, pills, geltabs, capsules or equivalent in a compartment in total have:

(i) between about 2 to 80 mg, 4 to 40 mg, 5 to 25 mg, or 10 to 20 mg IR propranolol, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of IR propranolol, or up to triple these amounts, or between about 6 and 240 mg; and

between about 2 to 80 mg, 4 to 40 mg, 5 to 25 mg, or 10 to 20 mg IR propranolol, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of DR propranolol, or up to triple these amounts, or between about 6 and 240 mg,

and optionally the morning or breakfast, or AM, tablet has approximately equal amounts of IR and DR propranolol; and

(ii) about between about 200 and 400 mg, between about 250 and 300 mg, about 170 mg, or about 340 mg, IR etodolac, or about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160 or 170 mg IR etodolac, or up to triple these amounts, or between about 180 and 1200 mg IP etodolac,

wherein optionally if there are two of the same tablets, pills, capsules, geltabs or equivalents are in a compartment, then the total dosage administration will be double the amount of what drug is in each tablet, pill, geltab, capsule or equivalent,

wherein optionally if there are three of the same tablets, pills, capsules, geltabs or equivalents are in a compartment, then the total dosage administration will be triple the amount of what drug is in each tablet, pill, geltab, capsule or equivalent.

13. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the membrane or coating:

(a) comprises between about 1% to 10% based on the weight of the bead, particle or the multilayered bead or particle;

(b) comprises approximately 1.5% to 6% based on the weight of the bead, particle or the multilayered bead or particle in a delayed (or controlled) release (DR) propranolol formulation.

14. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the water insoluble polymer comprises an ethylcellulose having a viscosity of not more than 30 cps when tested on a 5% solution at 25°C.

15. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the total amount of:

(a) the delayed (or controlled) release (DR) propranolol formulation and/or the immediate release (IR) propranolol formulation in the first formulation (optionally as one,

two or three or more tablets, pills, geltabs, capsules or equivalents) are each or are in total from between about 2 to 80 mg, between about 4 to 40 mg, between about 5 to 25 mg, or between about 10 to 20 mg, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg, or up to triple of each of these amounts, or between about 6 mg to about 240 mg DR propranolol,

and optionally the DR and IR formulations are present in the first formulation in approximately equal amounts; and/or

(b) the immediate release (IR) etodolac formulation in the first formulation is from between about 25 mg to 200 mg, 50 mg to 175 mg, 60 mg to 160 mg, or 70 mg to 150 mg, or about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160 or 170 mg, or up to triple of each of these amounts, or between about 75 mg and 450 mg,

wherein optionally the first formulation comprises:

(i) about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg, or between about 3 and 32 mg, of the delayed (or controlled) release (DR) propranolol formulation, or up to triple of each of these amounts, or between about 6 and 60 mg;

(ii) about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg, or between about 3 and 32 mg, of the immediate release (IR) propranolol formulation, or up to triple of each of these amounts, or between about 6 and 60 mg; and,

(iii) about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160 or 170 mg of the immediate release (IR) etodolac formulation, or up to triple of each of these amounts, or between about 120 and 510 mg,

and optionally all of (i), (ii), and (iii) are separately formulated in one, two or three or more tablets, pills, geltabs, capsules or equivalents,

and optionally the immediate release (IR) propranolol formulation comprises the racemic R(+) and S(–) mixture of propranolol, the substantially pure (S)-enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, coated on microbeads or particles or equivalents, optionally polysaccharide microbeads,

and optionally the delayed (or controlled) release (DR) propranolol formulation comprises the racemic R(+) and S(–) mixture of propranolol, the substantially pure (S)-

enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, coated on microbeads or particles or equivalents, optionally polysaccharide microbeads or particles, and further comprising an ammonio methacrylate copolymer dispersion or equivalents (optionally a EUDRAGIT® polymer or equivalents) also coated on the microbeads or microparticles or equivalents,

wherein optionally if two morning or AM tablets, pills, geltabs, capsules or equivalents have each 32 mg propranolol in each tablet, then the two tablets in the AM compartment total a 64 mg etodolac dosage administration for the AM, and if three morning or AM tablets, pills, geltabs, capsules or equivalents have each 32 mg propranolol in each tablet, then the three tablets in the AM compartment total a 96 mg etodolac dosage administration for the AM.

16. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the water-soluble polymer has a viscosity of not more than 200 cps when tested on a 2% aqueous solution at 25°C.

17. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein:

the racemic R(+) and S(–) mixture of propranolol, the substantially pure (S)-enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, in the delayed (or controlled) release (DR) propranolol formulation and/or the immediate release (IR) propranolol formulation are contained in or adsorbed to or onto a core,

wherein optionally the core comprises a plurality of sugar spheres, wherein optionally the sugar spheres comprise sugar spheres PF006® or SUGLETS®, and optionally the amount of sugar spheres in the formulation or in each dosage unit is about 21%(w/w), or is between about 20 to 22%(w/w), or is between about 18 to 25%(w/w).

18. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein:

the racemic R(+) and S(–) mixture of propranolol, the substantially pure (S)-enantiomer of propranolol, or the pharmaceutically acceptable salt thereof, or mixtures thereof, in the delayed (or controlled) release (DR) propranolol formulation and/or the immediate release (IR) propranolol formulation is coated with a coating agent,

and optionally with the coating agent the delayed (or controlled) release (DR) propranolol formulation and/or the immediate release (IR) propranolol formulation forms a bead or a pellet,

and optionally the coating agent comprises a water soluble cellulose ether and/or OPADRY®,

and optionally the water soluble cellulose ether comprises a hypromellose, optionally a METHOCEL E5 PREMIUM LV™,

wherein optionally the coating agent comprises both the hypromellose and the water soluble cellulose ether, optionally OPADRY®, and optionally the hypromellose and the water soluble cellulose ether (optionally OPADRY®, are present in approximately equal amounts in the formulation or each dosage unit;

and optionally the coating agent further comprises about 2.5%(w/w), or between about 2%(w/w) to 3%(w/w), or between about 1%(w/w) to 4%(w/w), of the formulation or each dosage unit.

19. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of claim 17, wherein the coating agent in the delayed (or controlled) release (DR) propranolol formulation further comprises a triethyl citrate, an ammonio methacrylate copolymer dispersion Type A (optionally EUDRAGIT® RL-30D), an ammonio methacrylate copolymer dispersion Type B (optionally EUDRAGIT ® RS-30D), or a mixture thereof,

and optionally the coating agent comprises: the hypromellose at between about 1%(w/w) and 1.5%(w/w); the OPADRY® at between about 1%(w/w) and 1.5%(w/w); the ammonio methacrylate copolymer dispersion Type A at between about 0.5%(w/w) to 1.5%(w/w); the ammonio methacrylate copolymer dispersion Type B at between about 8%(w/w) to 9%(w/w) or 7%(w/w) to 10%(w/w); and the triethyl citrate at between about 1%(w/w) to 2%(w/w), of the formulation or each dosage unit,

and optionally the formulation or each dosage unit further comprises a neutral filler, optionally at an amount of between about 5%(w/w) to 6%(w/w), or about 3%(w/w) to 8%(w/w), of the formulation or each dosage unit,

and optionally the neutral filler comprises a talc or a hydrated magnesium silicate.

20. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the racemic R(+) and S(–) mixture of etodolac, the substantially pure (S)-enantiomer of etodolac, or the pharmaceutically acceptable salt thereof, or mixtures thereof, in the immediate release (IR) etodolac formulation comprises a granulated etodolac, or is comprised substantially of granulated etodolac.

21. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the immediate release (IR) etodolac formulation comprises or is formulated with a filler, a disintegrant a glidant and/or a lubricant,

and optionally: the filler comprises a microcrystalline cellulose (optionally an AVICEL PH101®); the disintegrant comprises a croscarmellose sodium (optionally an Ac-Di-Sol®); the glidant comprises a colloidal silicon dioxide (optionally a Cab-O-Sil® M5P®), and/or the lubricant comprises magnesium stearate or equivalent thereof,

and optionally in the formulation or each dosage unit: the filler is in an amount at between about 4%(w/w) to 5%(w/w) or 3%(w/w) to 6%(w/w); the disintegrant is in an amount at between about 2%(w/w) to 3%(w/w) or 1%(w/w) to 4%(w/w); the glidant is in an amount at between about 0.1%(w/w) to 0.5%(w/w); and/or, the lubricant is in an amount at between about 0.1%(w/w) to 0.5%(w/w).

22. A method of chronodosing an individual with: a racemic R(+) and S(–) mixture of propranolol, a substantially pure (S)-enantiomer of propranolol, or a pharmaceutically acceptable salt thereof, or mixtures thereof; and, a racemic R(+) and S(–) mixture of etodolac, a substantially pure (S)-enantiomer of etodolac, or a pharmaceutically acceptable salt thereof, or mixtures thereof, comprising:

administering to the individual a pharmaceutical dosage form, a drug delivery device or a product of manufacture of any of the preceding claims.

23. A method for treating or ameliorating a cancer, tumor or a dysfunctional cell condition, or a symptom of cancer, tumor or a dysfunctional cell condition, comprising administering or delivering to an individual in need thereof a pharmaceutical dosage form, a drug delivery device or a product of manufacture of any of the preceding claims,

wherein optionally a lymphocyte-to-monocyte ratio (LMR) of less than 6 or less than 5 or less than 4 or less than 3, is used to select an individual in need thereof; or, a C-reactive protein (CRP)/Albumin ratio of greater than 0.05 or greater than 0.8 or greater than 0.10 or greater than 0.12 or greater than 0.15 or greater 0.18, is used to select an individual in need thereof; or, a neutrophil-to-lymphocyte ratio (NLR) of greater than 2.0 or greater than 3.0 or greater than 4.0 or greater than 5.0, is used to select an individual in need thereof,

wherein optionally the pharmaceutical dosage form, drug delivery device or product of manufacture is administered in conjunction with or as an adjunct therapy with another treatment for cancer,

wherein optionally the pharmaceutical dosage form, drug delivery device or product of manufacture is administered is delivered or administered to the individual in need thereof before, at the same time and/or after the other treatment for cancer.

24. The method of claim 24, wherein the therapeutic combination is administered at a dosage regimen of:

(a)

- one, two or three or more tablets, pills, capsules, geltabs or equivalents for administration in the morning or breakfast, or AM, that each tablet, pill, geltab, capsule or equivalent has, or all tablets, pills, geltabs, capsules or equivalent in a compartment in total have: 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or 32 mg of immediate release (IR) propranolol; 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 21, 22, 23,

24, 25, 26, 27, 28, 29, 30, 31or 32 mg of delayed (or controlled) release (DR) propranolol; and about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 mg IR etodolac,

and optionally the morning or breakfast, or AM one, two or three or more tablets, pills, capsules, geltabs or equivalents have approximately equal amounts of IR and DR propranolol (optionally about 16 mg IR and 16 mg DR propranolol for a racemic mixture, or 4 to 8 mg IR and 4 to 8 mg DR propranolol for a substantially pure (S)-enantiomer, of propranolol); and

one, two or three or more tablets, pills, capsules, geltabs or equivalents for administration in at dinnertime or the evening (e.g., PM or bedtime) each having or in total having between about 100 and 250 mg, between about 200 and 400 mg, between about 250 and 300 mg, about 270 mg, or about 200, 210, 220, 225, 230, 240, 250, 260, 270, 275, 280, 290, 300, 310, 320, 330, 340 or 350 mg, IR etodolac; or

(b)

- one, two or three or more tablets, pills, capsules, geltabs or equivalents for administration in the morning or breakfast, or AM, that each tablet, pill, geltab, capsule or equivalent has, or all tablets, pills, geltabs, capsules or equivalent in a compartment in total have:

(i) between about 2 to 80 mg, 4 to 40 mg, 5 to 25 mg, or 10 to 20 mg IR propranolol, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of IR propranolol, or up to triple these amounts, or between about 6 and 240 mg; and

between about 2 to 80 mg, 4 to 40 mg, 5 to 25 mg, or 10 to 20 mg IR propranolol, or about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg of DR propranolol, or up to triple these amounts, or between about 6 and 240 mg,

and optionally the morning or breakfast, or AM, tablet has approximately equal amounts of IR and DR propranolol; and

(ii) about between about 200 and 400 mg, between about 250 and 300 mg, about 170 mg, or about 340 mg, IR etodolac, or about 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160 or 170 mg IR etodolac, or up to triple these amounts, or between about 180 and 1200 mg IP etodolac,

wherein optionally if there are two of the same tablets, pills, capsules, geltabs or equivalents are in a compartment, then the total dosage administration will be double the amount of what drug is in each tablet, pill, geltab, capsule or equivalent,

wherein optionally if there are three of the same tablets, pills, capsules, geltabs or equivalents are in a compartment, then the total dosage administration will be triple the amount of what drug is in each tablet, pill, geltab, capsule or equivalent.

25. The pharmaceutical dosage form, the drug delivery device or the product of manufacture of any of the preceding claims, wherein the water insoluble polymer comprises an ethylcellulose having a viscosity of not more than 30 cps when tested on a 5% solution at 25°C.

26. A drug delivery device or package, a blister package, a clamshell or a tray, comprising a pharmaceutical dosage form or formulation of any of the preceding claims, wherein the drug delivery device or package, blister pack, clamshell or tray comprises a plurality of compartments spatially arranged on the drug delivery device or package, blister pack, clamshell or tray to follow a dosage administration regimen,

wherein the spatially arranged plurality of compartments are in at least two rows, each row marked for the time for which the tablets, pills, capsules, geltabs or equivalents are to be taken by a user (optionally a patient), optionally one row marked for morning, breakfast or AM administration, and one row marked for evening, dinnertime or PM administration, and optionally the row or rows marked for morning, breakfast or AM administration is or are positioned above the row or rows marked for evening, dinnertime or PM administration,

and optionally the spatially arranged plurality of compartments are in four rows, two rows marked for morning, breakfast or AM administration, and two rows marked for evening, dinnertime or PM administration,

and optionally each row comprises seven compartments for one dosage administration for each day of the week, or eight compartments for one dosage administration for each day of the week and one spare, and optionally each vertically arranged set of compartments, or columns, are marked for which day of the week the dosage formulations contained therein are to be taken by the user, and optionally where

the drug delivery device or package, blister pack, clamshell or tray has one row for morning, breakfast or AM administration, and one row marked for evening, dinnertime or PM administration, each column or day will have two compartments, optionally where the compartment for morning, breakfast or AM administration is above the compartment for evening, dinnertime or PM administration, and optionally the rows of compartments on the drug delivery device or package, blister package, clamshell or tray is arranged as set forth in FIG. 2,

and optionally each compartment has a foil or equivalent backing, or each compartment is an environmentally- (optionally moisture-, pathogen-, and/or light-) protected or sealed storage unit, and optionally the foil backing requires minimal finger strength to remove a dosage formulation (optionally one, two or three or more capsules, tablets, pills, geltabs or equivalents) in the compartment;

and optionally the blister package is a face seal blister package, a gang run blister package, a mock blister package, an interactive blister package or a slide blister package,

and optionally the drug delivery device or package, blister package, clamshell or tray is joined with board material which allows the product to be packaged, handled, hung, displayed and/or shipped without damaging the blister protection or seal, and optionally also provided with child resistant features,

and optionally the drug delivery device or package, blister package, clamshell or tray comprises a medical electronic monitory system that records administration time and transmits information to near-field communication (NFC) enabled mobile phone.

27. Use of the therapeutic combination of any of the preceding claims, in the manufacture of a medicament for treating or ameliorating a cancer, tumor or a dysfunctional cell condition, or a symptom of cancer, tumor or a dysfunctional cell condition.

28. A pharmaceutical dosage form, a drug delivery device or package, a blister package, a clamshell or a tray, or a product of manufacture of any of the preceding claims, for use in treating or ameliorating a cancer, tumor or a dysfunctional cell condition, or a symptom of cancer, tumor or a dysfunctional cell condition.

29. The pharmaceutical dosage form, drug delivery device or package, blister package, clamshell or tray, or product of manufacture of any of the preceding claims, further comprising an additional drug or active agent,

wherein optionally the additional drug or active agent comprises a cancer drug or a cancer adjunctive or support therapy,

and optionally the additional drug or active agent comprises, or the cancer drug or a cancer adjunctive or support therapy comprises:

a calcitriol (also called 1,25-dihydroxycholecalciferol), or ROCALTROL™, CALCIJEX™, or DECOSTRIOL™,

a gemcitabine-based therapy, optionally gemcitabine (e.g., GEMZAR™) alone; gemcitabine and paclitaxel; gemcitabine, paclitaxel and platinum; gemcitabine and lipo-platinum (e.g., NC-6004, a micellar nanoparticle product of cisplatin); gemcitabine and capecitabine; gemcitabine and S1 (S1 is the combination drug tegafur/ gimeracil/ oteracil, trade name TEYSUNO™); and/or, a nucleoside analog of gemcitabine such as NUC-1031 (ACELARIN®),

a 5-flurouracil (5-FU) based therapy, optionally capecitabine (e.g., XELODA™) alone; "FOLFIRI" treatment (a combination of folinic acid, or leucovorin, a vitamin B derivative; 5-flurouracil; and, irinotecan (e.g., CAMPTOSAR™), a topoisomerase inhibitor), optionally with liposomal irinotecan (e.g., ONIVYDE™); "FOLFOX" treatment (a combination of folinic acid, or leucovorin, a vitamin B derivative; 5-flurouracil; and, oxaliplatin (e.g., ELOXATIN™); "FOLFIRINOX" treatment (a combination of folinic acid, or leucovorin, a vitamin B derivative; 5-flurouracil; irinotecan (e.g., CAMPTOSAR™), a topoisomerase inhibitor; and, oxaliplatin (e.g., ELOXATIN™)); the nucleoside analog of 5-FU NUC-3373; a recombinant human hyaluronidase enzyme (e.g. PEGPH20™); and/or tifluridine and/or tipiracil (e.g., LONSURF™),

a tyrosine kinase inhibitor (TKI), optionally a sorafenib (e.g. NEXAVAR™), regorafenib (e.g. STIVARGA™), levantinib (e.g., LENVIMA™), cabozanitinib (e.g., CABOMETYX™, COMETRIQ™), ibrutinib (e.g. IMBRUVICA™), apatinibi and/or BGB-3111,

a PARP inhibitor (inhibitors of the enzyme poly ADP ribose polymerase), optionally olaparib (LYNPARZA™); rucaparib (e.g., RUBRACA™); niraparib (e.g., ZEJULA™); talazoparib; fluzoparib; AZD2281 (e.g., OLAPARIB™); ABT-888 (e.g., VELIPARIB™); AG014699 (e.g., RUCAPARIB™), simmiparib, SC-10914, CEP-8983, and/or BGB-290,

a Programmed cell Death protein 1 (PD1) inhibitor, optionally nivolumab (e.g., OPDIVO™); pembrolizumab (e.g., KEYTRUDA™); avelumab (e.g., BAVENCIO™); durvalumab (e.g., IMFINZI™); atezolizumab (e.g., TECENTRIQ™); BGB-A317; MGA012; GLS-010; SHR-120; CK-301 and/or HTI-1316,

a programmed death-ligand 1 (PDL1) inhibitor, optionally atezolizumab (e.g., TECENTRIQ™); avelumab (e.g., BAVENCIO™); durvalumab (e.g., IMFINZI™); and/or HTI-1316,

a drug that inhibits cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), optionally ipilimumab (e.g., YERVOY™) or tremelimumab.

an "immuno-oncology" therapy, optionally a treatment for an oncolytic virus, or an autologous formula fixed tissue vaccine, or immune checkpoint inhibitors, optionally ipilimumab; tremelimumab; and/or nivolumab (e.g., OPDIVO™),

a treatment or amelioration for a neuroendocrine tumor or a carcinoid or a side effect caused by the carcinoid or neuroendocrine tumor; optionally, a drug that is an analog of somatostatin such as e.g., the peptide H-D-2Nal-Cys(1)-Tyr-D-Trp-Lys-Val-Cys(1)-Thr-NH2, or lanreotide or lanreotide acetate or lanreotide SR (e.g., SOMATULINE™), manufactured e.g., by Ipsen (Paris, France); or, octreotide (e.g., SANDOSTATIN™) or octreotide acetate LAR (SANDOSTATIN LAR™, Novartis Pharma AG),

an anti-microtubule agent including at least one of, or any one of: a paclitaxel (e.g. TAXOL™ or GENEXOL™), a paclitaxel protein bound particles (e.g. ABRAXANE™), a polymeric micelle paclitaxel (GENEXOL PM™), a polymeric micelle paclitaxel manufactured by Shanghai Yizhong Biotechnology Co., Ltd (as described, e.g., in China patent no. CN 102218027 B), a liposomal paclitaxel (e.g. LIPUSU™), a docetaxel (e.g., TAXOTERE™), a DHP107, an oral paclitaxel and P-gp inhibitor HM30181A (e.g. ORAXOL™), a polymeric micelle docetaxel (e.g.

NANOXEL PM™), a cabazitaxel (e.g. JEVTANA ™), a polymeric micelle cabazitaxel, a vincristine, a vinblastine, a vinorelbine (e.g. NAVELBINE™), a vinflunine, and/or an eribulin (e.g. HALAVEN™), or any combination thereof,

an alkylating agent including at least one of, or any one of: a cisplatin (e.g. PLATINOL™), a carboplatin (e.g. PARAPLATIN™), oxaliplatin (e.g., ELOXATIN™), a NC-6004 (e.g. LIPOPLATIN ™), an oxaliplatin (e.g., ELOXATIN™), a bendamustine (e.g., TREANDA™), a cyclophosphamide, an ifosfamide, a chlorambucil, a melphalan, a dacarbazine, a mitozalomide, and/or a temozolomide, or any combination thereof,

a cytotoxic antibiotic including at least one of, or any one of: a doxorubicin (e.g. ADRIAMYCIN™ or RUBEX™), a pegylated liposomal doxorubicin (e.g. DOXIL™ or LIPODOX ™), a non-pegylated liposomal doxorubicin (e.g. MYOCET ™), a polymeric micelle doxorubicin, a daunorubicin, a liposomal daunorubicin, an epirubicin (e.g. ELLENCE™), an idararubicin, a piranubicin, an aclarubicin, a mitoxantrone, a bleomycin, and/or a mitomycin, or any combination thereof,

a topisomerase inhibitor including at least one of, or any one of: an irinotecan (e.g., CAMPTOSAR™), a liposomal irinotecan (e.g., ONIVYDE™), an etirinotecan pegol, (e.g. ONZEALD™), a liposomal encapsulated irinotecan and 5FU (e.g. CPX-1), a topotecan, a camptothecin and/or an etoposide (e.g. ETOPOPHOS™), or any combination thereof,

an anti-metabolite including at least one of, or any one of: a methotrexate, a pemetrexed (e.g. ALIMTA™), a pralatrexate (e.g. FOLOTYN™), a 5-fluorouracil or 5-FU (e.g. ADRUCIL™), a capecitabine (e.g., XELODA™), a tegafur/gimeracil/oteracil (e.g. TEYSUNO™ or S-1™), a trifluridine/tipiracil (e.g. LONSURF™), a gemcitabine (e.g. GEMZAR™), a NUC-1031 (e.g. ACELARIN™), and/or a azacytidine (e.g. VIDAZA™) and a hydroxycarbamide, or any combination thereof,

and optionally the cancer drug or a cancer adjunctive or (as a drug or pharmaceutical) support therapy is formulated with the first formulation and/or the second formulation, or the cancer drug or a cancer adjunctive or (as a drug or pharmaceutical) support therapy is separately formulated, wherein optionally the cancer

drug or a cancer adjunctive or (as a drug or pharmaceutical) support therapy is formulated in the form of a tablet, pill, geltab, capsule and the like which is placed or inserted in the same compartment on a blister card, clamshell or tray or equivalent with one or more tablets, pills, geltabs, capsules and the like comprising a first formulation and/or second formulation, wherein all tablets, pills, geltabs, capsules and the like in the same compartment are to be taken at the same time by a user, optionally, a patient.

30. The use or pharmaceutical dosage form, or the drug delivery device or the product of manufacture of any of the preceding claims, wherein the cancer or tumor or dysfunctional cell condition(s) is or are: neuroendocrine tumors, cancers of the endocrine system, and pancreatic cancer, including gastroenteropancreatic neuroendocrine tumors (GEP-NET), pancreatic neuroendocrine tumors (PanNETs), islet cell tumors or non-islet hypoglycemic cell tumor, intestinal endocrine tumors, carcinoids, adenocarcinoma pancreatic tumors, pheochromocytoma (PCC) or cancer of the adrenal gland, or cancer of the medulla of the adrenal glands, paraganglioma or chemodectoma, a gastrinoma (a gastrin secreting tumor), primary neuroendocrine carcinoma of the skin; hepatocellular carcinoma and liver cancers; brain and nerve cell cancers including neuroblastomas, brain stem glioma and glioblastoma multiforme; ovarian cancer; angiosarcoma; bone cancer and osteosarcoma; sarcomas, including bone and soft tissue sarcomas, chondrosarcoma, liposarcoma, rhabdomyosarcoma, Kaposi's sarcoma, desmoid tumor, epithelioid sarcoma, lymphangiosarcoma, and lymphosarcoma; familial adenomatous polyposis; lung cancers including small cell lung cancer and non-small cell lung cancer; skin cancer and melanomas, including cutaneous or intraocular melanoma, merkel-cell carcinoma (MCC); cancers of the head and neck; uterine cancer; rectal and colorectal cancer, including colon cancer and cancer of the anal region; stomach cancer; breast cancer; carcinoma of the fallopian tubes; carcinoma of the endometrium; carcinoma of the cervix; carcinoma of the vagina; carcinoma of the vulva; lymphomas, including chronic or acute leukemia, lymphocytic lymphomas, Hodgkin's Disease, primary CNS lymphoma; cancer of the esophagus; cancer of the small intestine; cancer of the thyroid gland or parathyroid gland, medullary thyroid cancer (MTC) or cancer of the parafollicular cells (C cells); cancer of the urethra; cancer of the penis; prostate cancer; cancer of the bladder; cancer of the kidney or ureter or renal cell carcinoma, or carcinoma of the renal pelvis; a neoplasm of the central nervous system (CNS); spinal axis tumors; pituitary adenoma; and, retinoblastoma; and any combination thereof.

FIG. 1

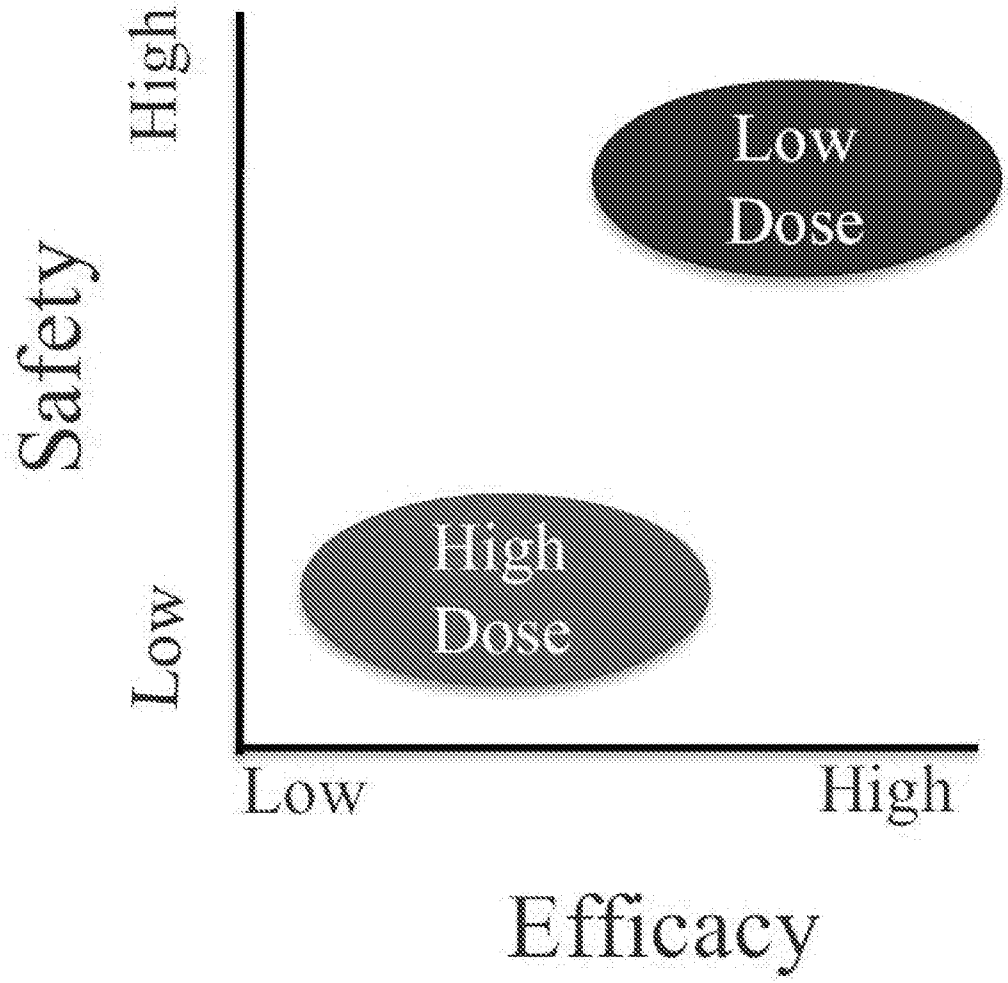


FIG. 2

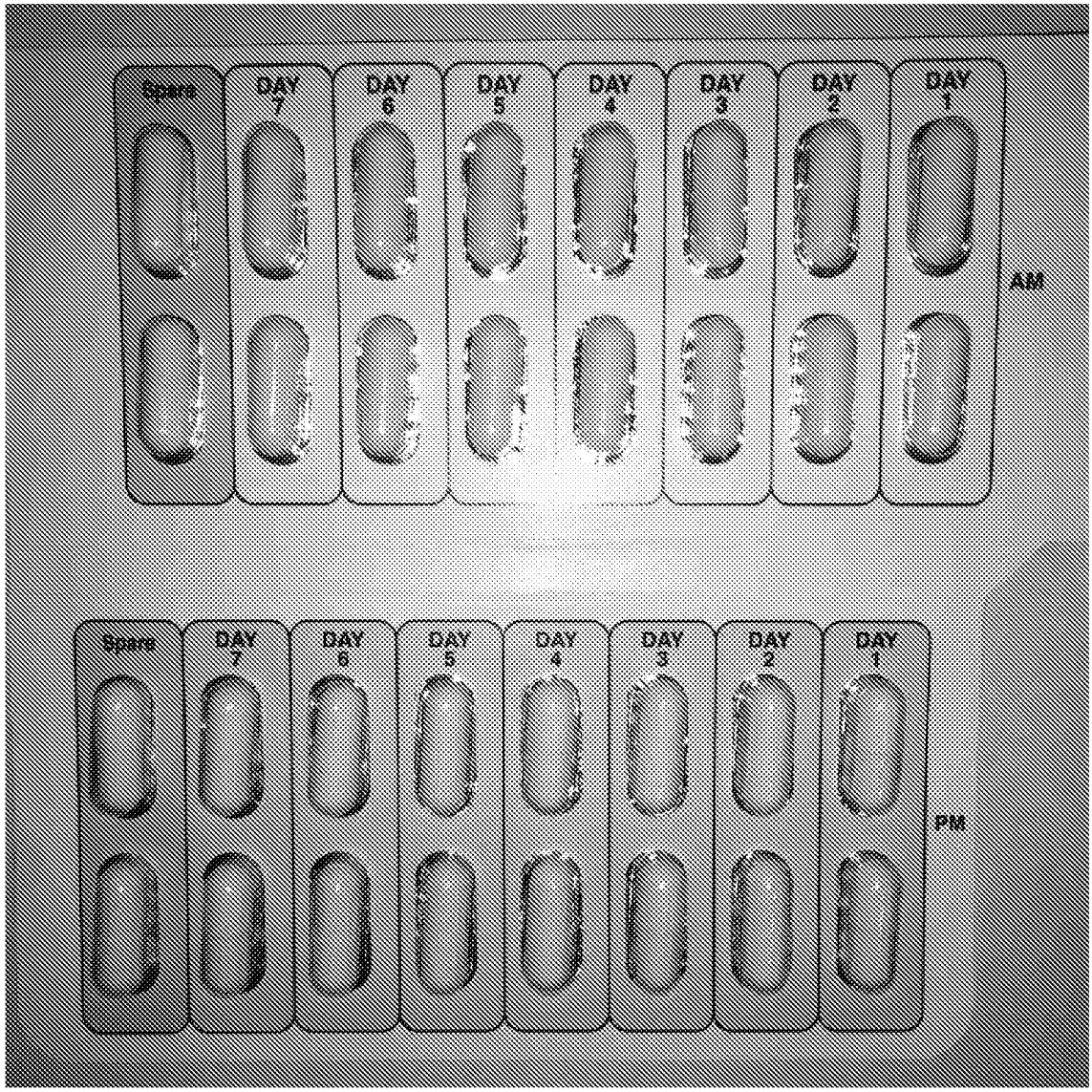
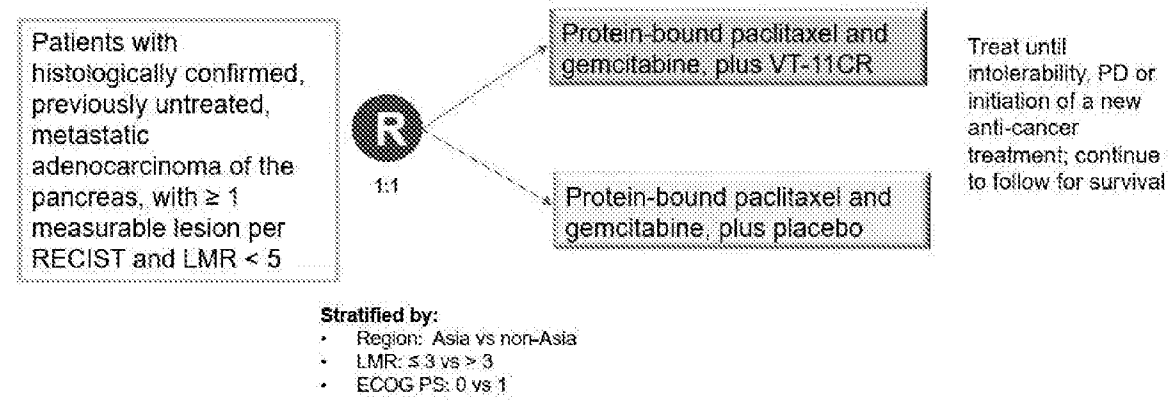

Spare
DAY 7
DAY 6
DAY 5
DAY 4
DAY 3
DAY 2
DAY 1
AM
Spare
DAY 7
DAY 6
DAY 5
DAY 4
DAY 3
DAY 2
DAY 1
PM

FIG. 3



Stratified by:

- Region: Asia vs non-Asia
- LMR: ≤ 3 vs > 3
- ECOG PS: 0 vs 1

ECOG = Eastern Cooperative Oncology Group
LMR = lymphocyte / monocyte ratio
PD = progressive disease
R = randomization
RECIST = Response Evaluation Criteria in Solid Tumors

FIG. 4

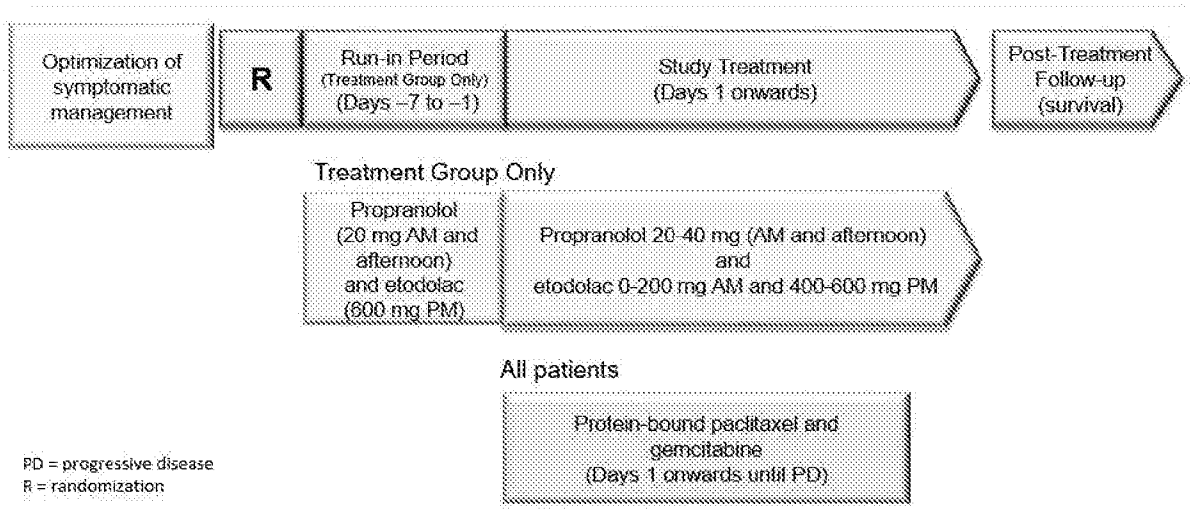
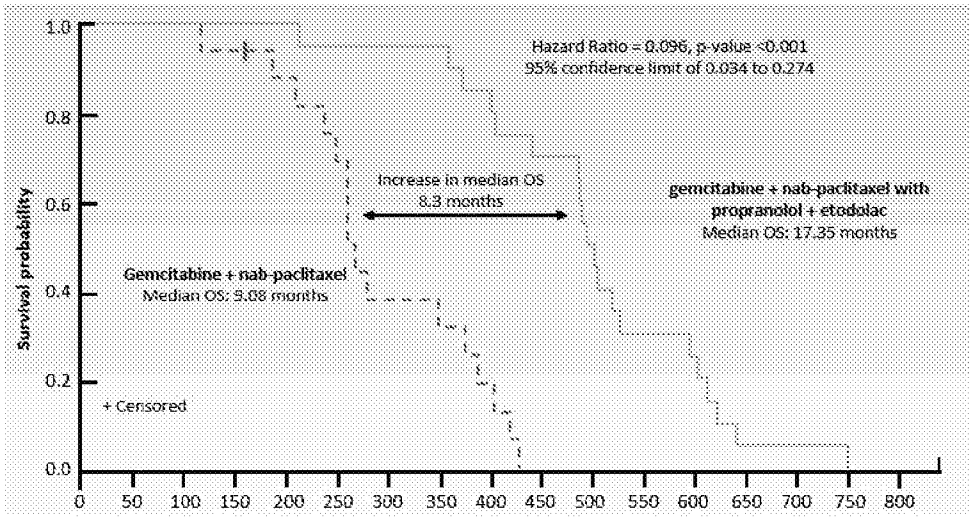

Optimization of symptomatic management
R
Run-in Period
(Treatment Group Only)
(Days –7 to –1)
Study Treatment
(Days 1 onwards)
Post-Treatment Follow-up (survival)
Treatment Group Only
Propranolol (20 mg AM and afternoon) and etodolac (600 mg PM)
Propranolol 20-40 mg (AM and afternoon) and etodolac 0-200 mg AM and 400-600 mg PM
All patients
Protein-bound paclitaxel and gemcitabine
(Days 1 onwards until PD)
PD = progressive disease
R = randomization

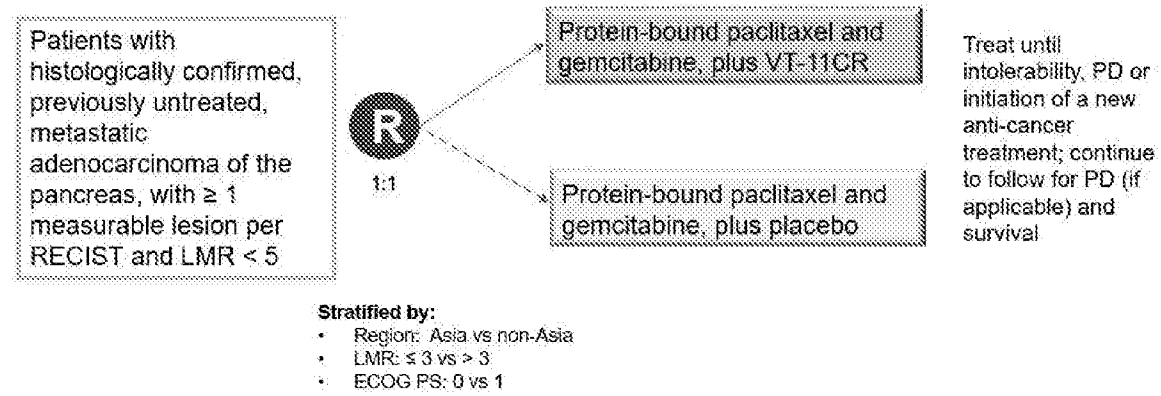
FIG. 5



OS=overall survival

Source: Vicus data on file (FEB 2016)

FIG. 6

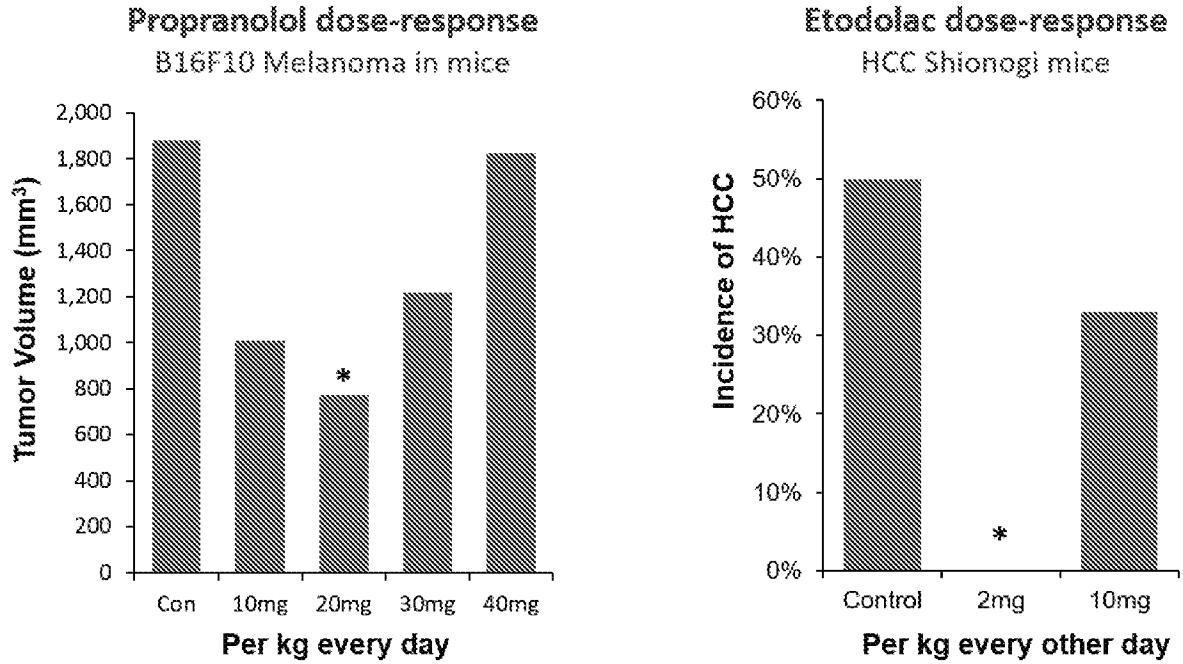


Stratified by:

- Region: Asia vs non-Asia
- LMR: ≤ 3 vs > 3
- ECOG PS: 0 vs 1

ECOG = Eastern Cooperative Oncology Group
LMR = lymphocyte / monocyte ratio
PD = progressive disease
R = randomization
RECIST = Response Evaluation Criteria in Solid Tumors

FIG. 7



* p<0.05 vs control

FIG. 8

Figure 1. Propranolol Individual Product (16 mg IR + 16 mg DR) Dissolution Profiles: 5 °C / Ambient RH

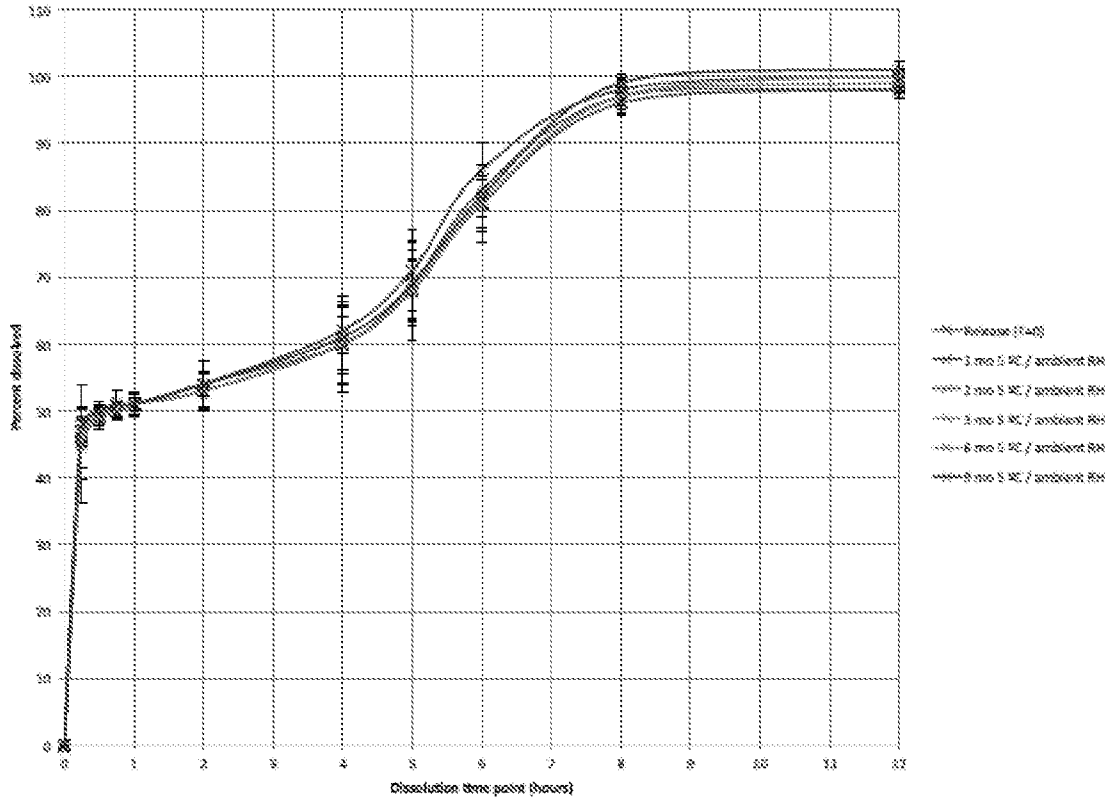


FIG. 9

Figure 2. Propranolol Individual Product (16 mg IR + 16 mg DR) Dissolution Profiles: 25 °C / 60% RH

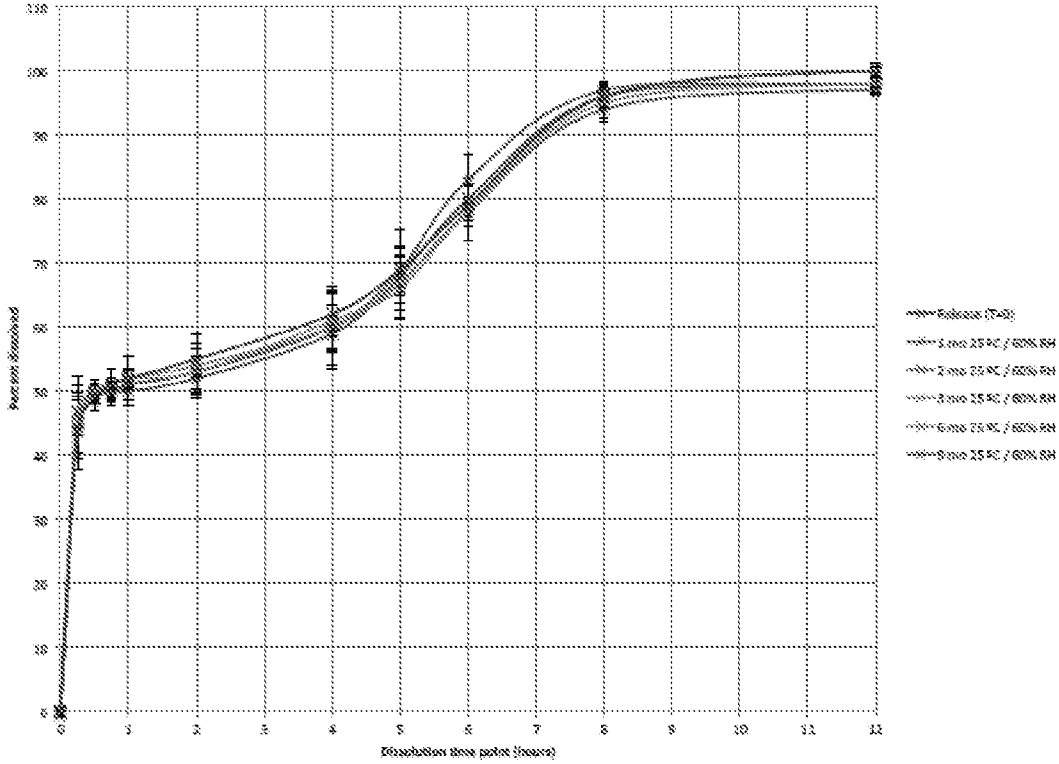


FIG. 10

Figure 3. Propranolol Individual Product (16 mg IR + 16 mg DR) Dissolution Profiles: 30 °C / 65% RH

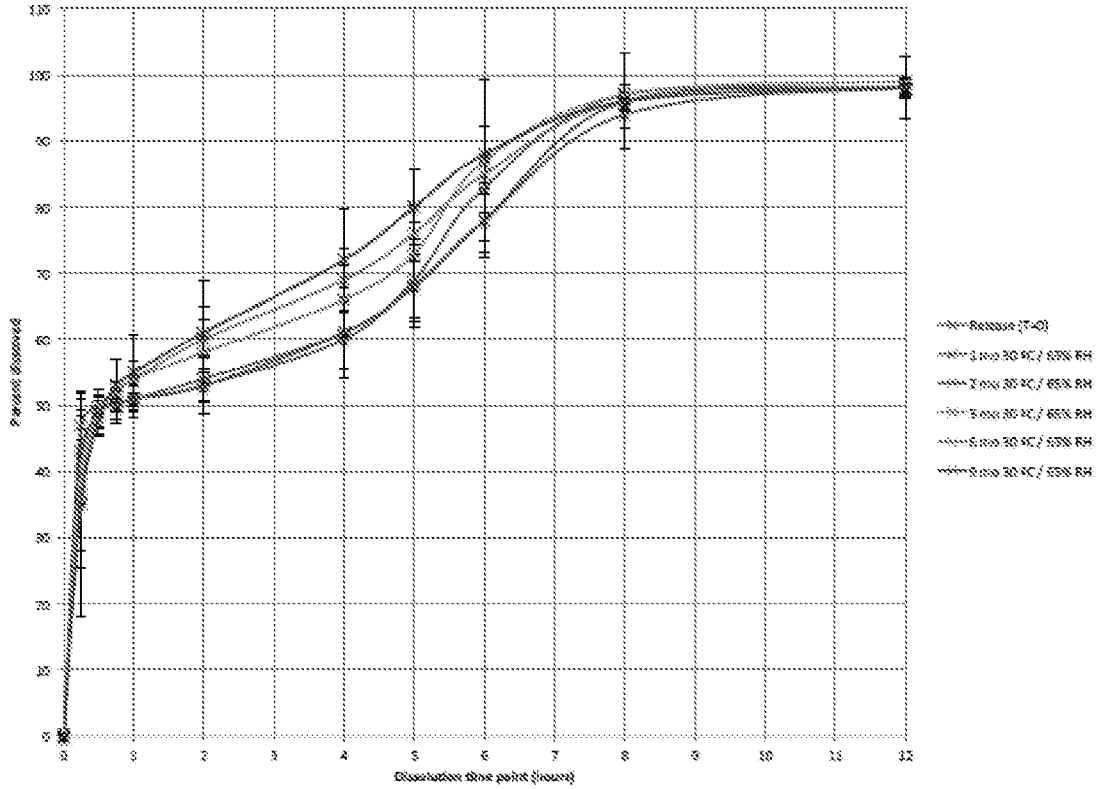


FIG. 11

Figure 4. Propranolol Individual Product (16 mg IR + 16 mg DR) Dissolution Profiles: 40 °C / 75% RH

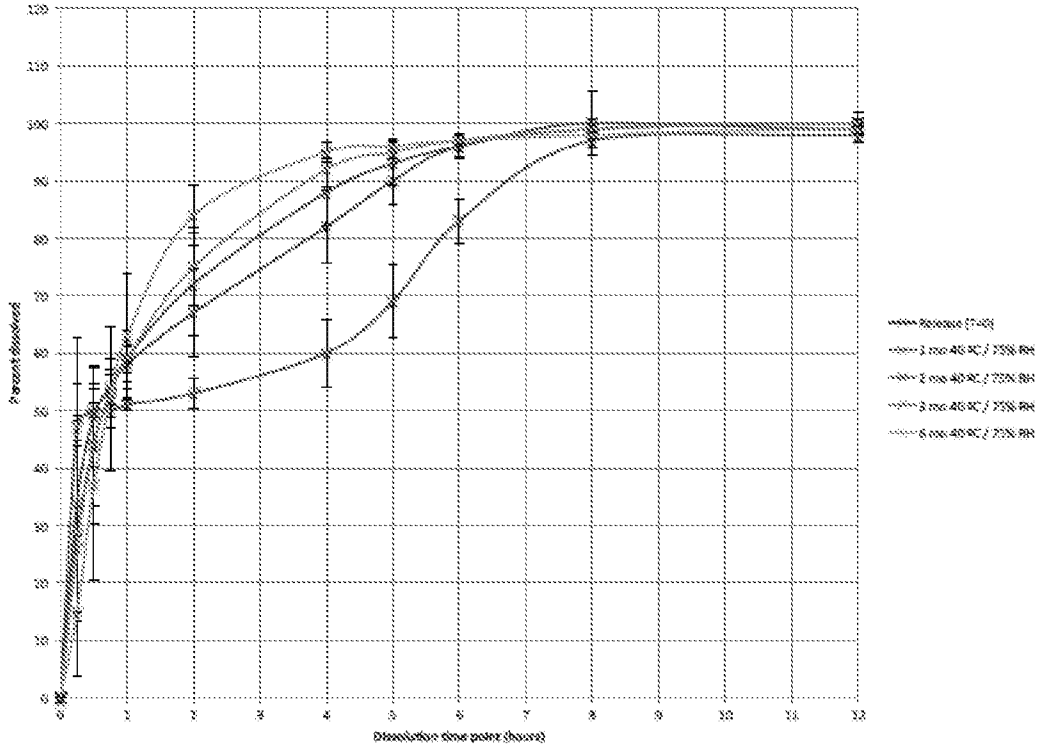


FIG. 12

Figure 6. Comparison of Propranolol Individual Product Dissolution Profiles at T=0, 9 Months at 5 °C and 9 Months at 25 °C / 60% RH for Assignment of Shelf Life and Short-Term Excursions

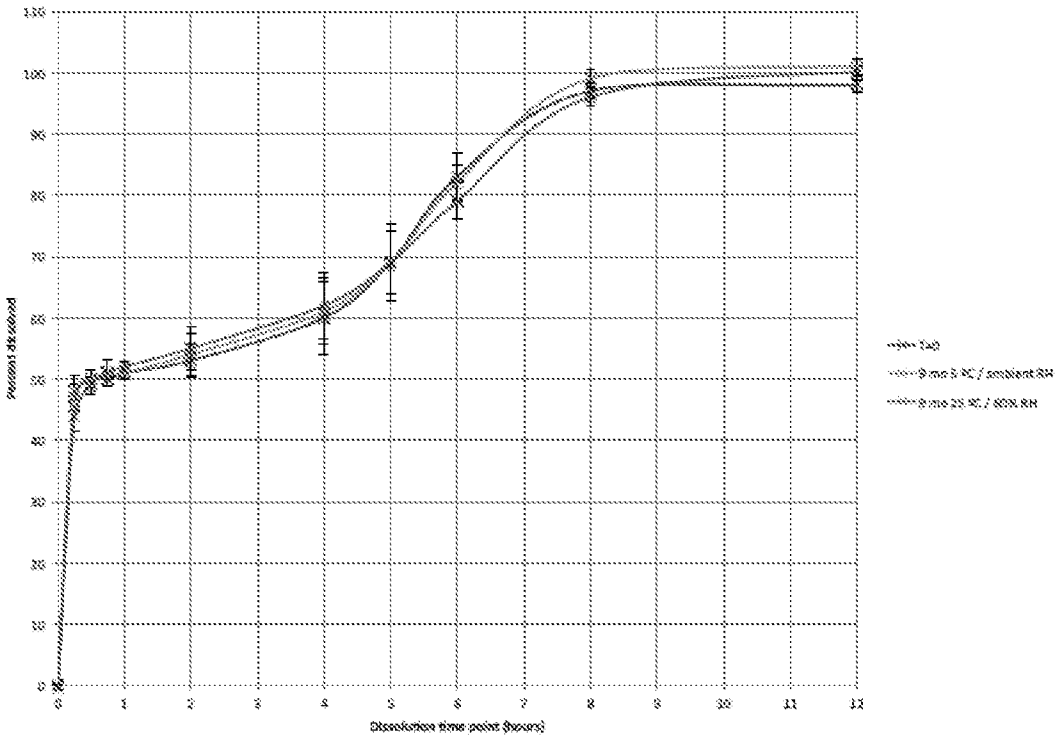


FIG. 13

Figure 7. Propranolol (16 mg IR + 16 mg DR) w/ Etodolac 70 mg Dissolution Profiles: 5 °C / Ambient RH

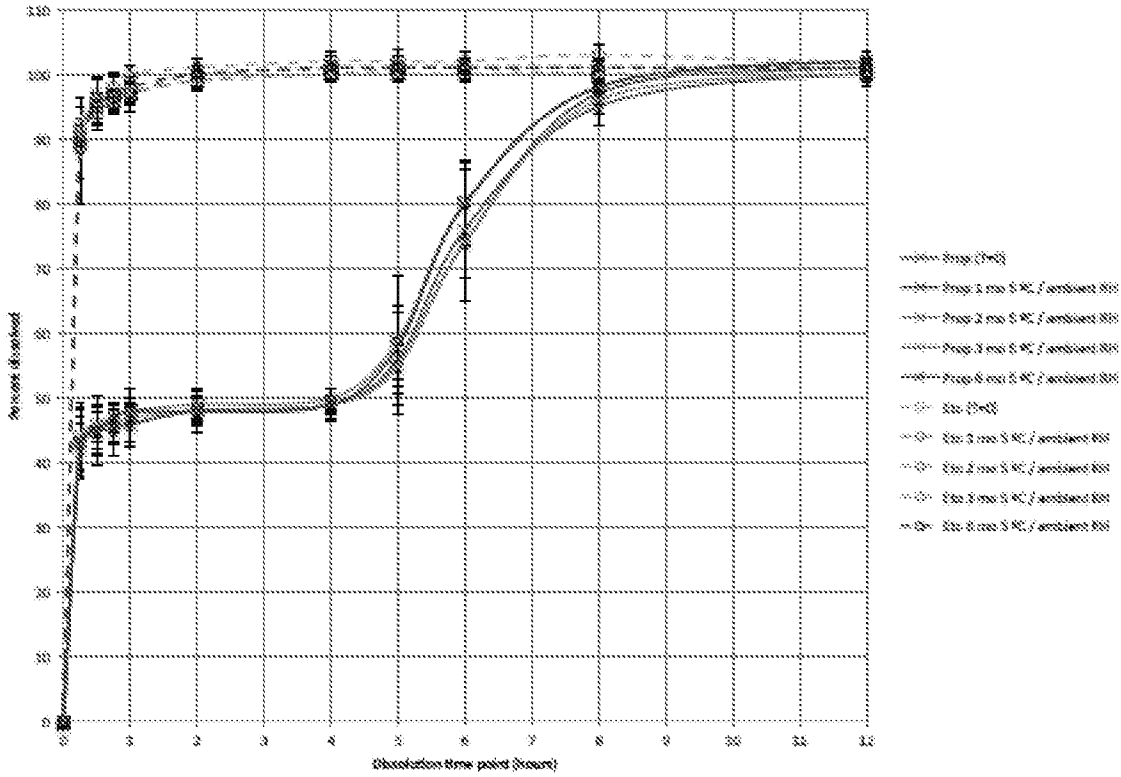


FIG. 14

Figure 8. Propranolol (16 mg IR + 16 mg DR) w/ Etodolac 70 mg Dissolution Profiles: 25 °C / 60% RH

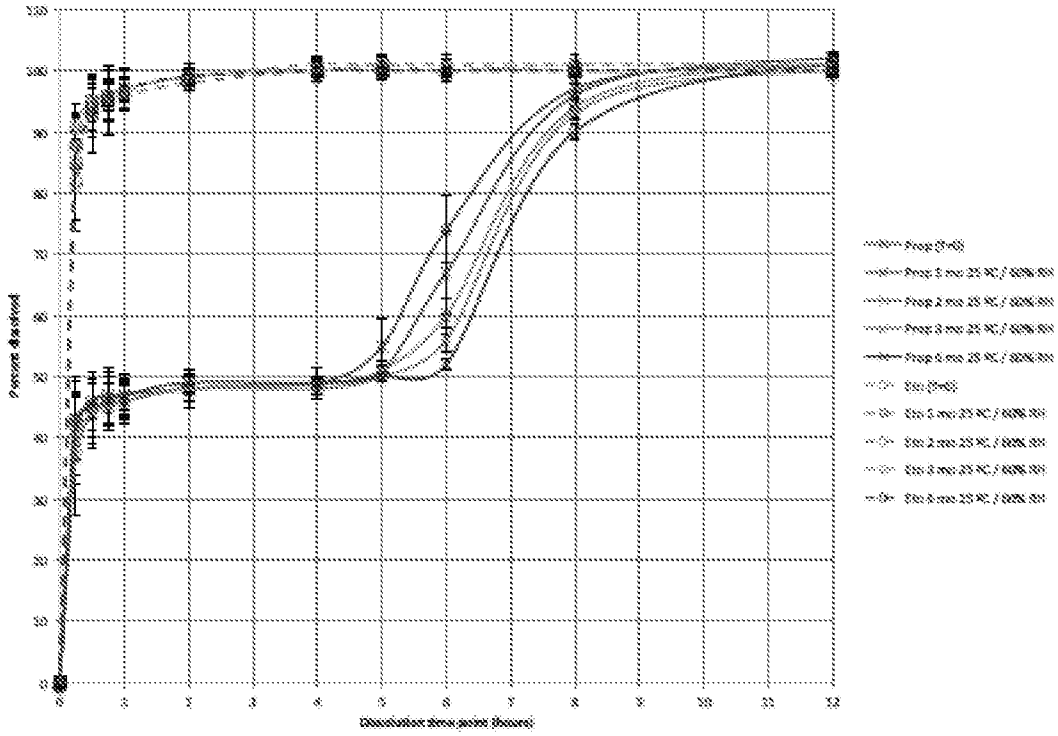


FIG. 15

Figure 9. Propranolol (16 mg IR + 16 mg DR) w/ Etodolac 70 mg Dissolution Profiles: 30 °C / 65% RH

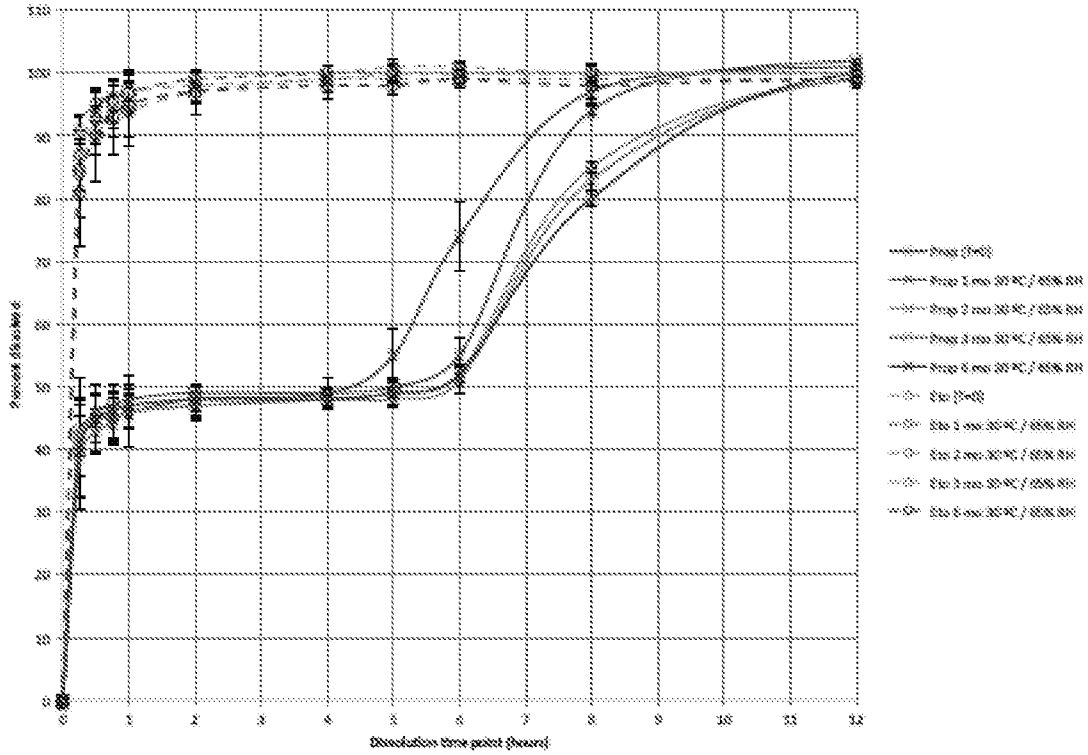


FIG. 16

Figure 16. Propranolol (16 mg IR + 16 mg DR) w/ Etodolac 70 mg Dissolution Profiles: 40 °C / 75% RH

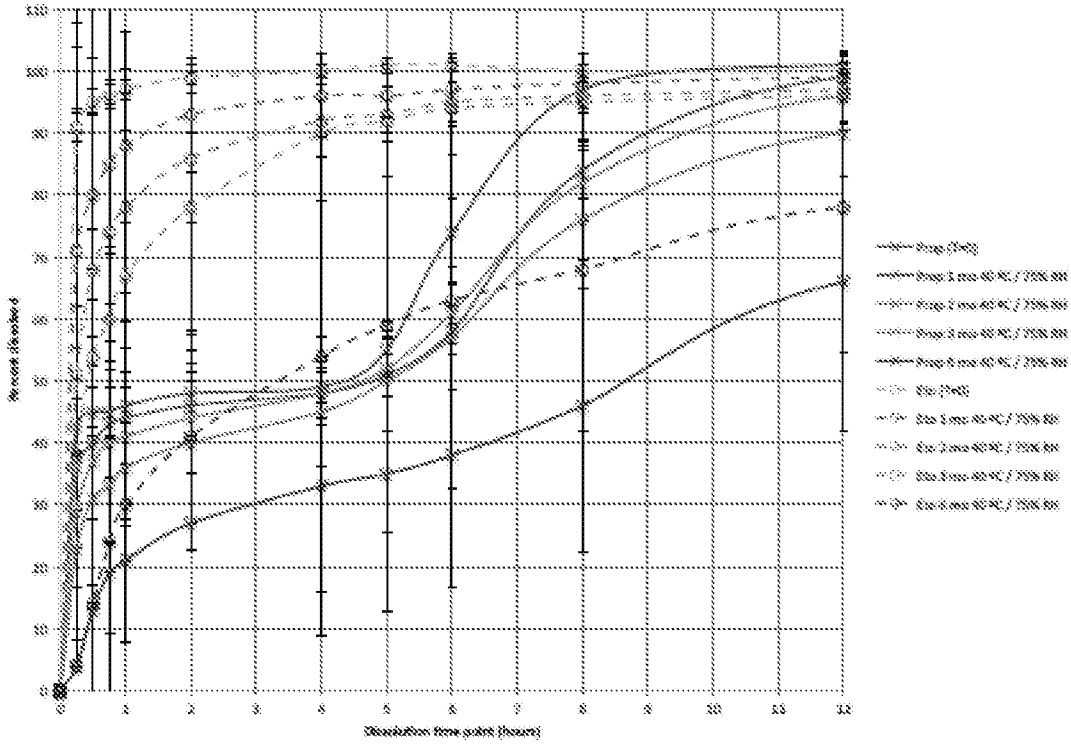


FIG. 17

Figure 12. Comparison of Combination Product Dissolution Profiles at T=0, 6 Months at 5 °C, and 1 Month at 25 °C / 60%RH for Assignment of Shelf Life and Short-Term Excursions

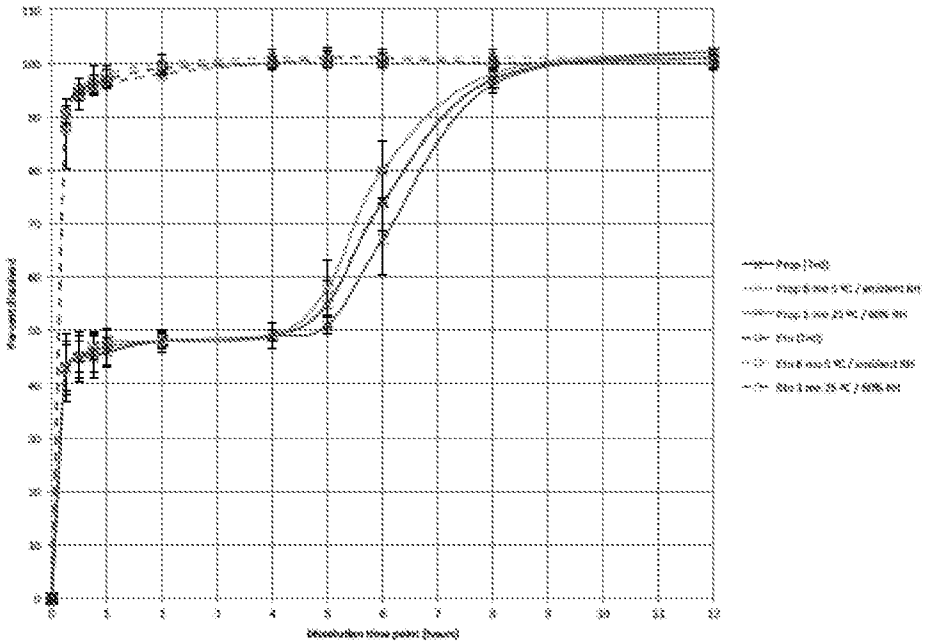


FIG. 18

	Dissolution 240min	Dissolution 300min	Dissolution 360min
Initial	Propranolol Mean: 49%, %RSD: 2.5	Propranolol Mean: 55%, %RSD: 4.4	Propranolol Mean: 74%, %RSD: 5.5

	5°C Chamber			25°C/60%RH Chamber			30°C/65%RH Chamber		
	240min	300min	360min	240min	300min	360min	240min	300min	360min
1 month	Propranolol Mean: 49%, %RSD: 2.3	Propranolol Mean: 56%, %RSD: 8.4	Propranolol Mean: 76%, %RSD: 10.9	Propranolol Mean: 49%, %RSD: 1.0	Propranolol Mean: 51%, %RSD: 1.6	Propranolol Mean: 67%, %RSD: 6.7	Propranolol Mean: 49%, %RSD: 0.6	Propranolol Mean: 50%, %RSD: 0.9	Propranolol Mean: 55%, %RSD: 2.9
2 month	Propranolol Mean: 49%, %RSD: 1.5	Propranolol Mean: 55%, %RSD: 3.3	Propranolol Mean: 74%, %RSD: 5.5	Propranolol Mean: 49%, %RSD: 0.7	Propranolol Mean: 51%, %RSD: 0.8	Propranolol Mean: 60%, %RSD: 2.9	Propranolol Mean: 48%, %RSD: 1.2	Propranolol Mean: 49%, %RSD: 2.3	Propranolol Mean: 54%, %RSD: 1.4
3 month	Propranolol Mean: 50%, %RSD: 1.6	Propranolol Mean: 59%, %RSD: 9.9	Propranolol Mean: 80%, %RSD: 6.4	Propranolol Mean: 48%, %RSD: 1.1	Propranolol Mean: 50%, %RSD: 0.9	Propranolol Mean: 56%, %RSD: 2.0	Propranolol Mean: 48%, %RSD: 1.1	Propranolol Mean: 48%, %RSD: 1.0	Propranolol Mean: 53%, %RSD: 2.2
6 month	Propranolol Mean: 49%, %RSD: 1.0 (U)	Propranolol Mean: 58%, %RSD: 5.1 (U)	Propranolol Mean: 80%, %RSD: 5.3 (U)	Propranolol Mean: 49%, %RSD: 1.1 (U)	Propranolol Mean: 50%, %RSD: 0.9 (U)	Propranolol Mean: 52%, %RSD: 0.8 (U)	Propranolol Mean: 48%, %RSD: 1.5 (U)	Propranolol Mean: 49%, %RSD: 0.9 (U)	Propranolol Mean: 52%, %RSD: 1.4 (U)


Fig. 19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/59047

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/138, 31/407; B65D 75/36 (2018.01)
CPC - A61K 31/138, 31/407; B65D 75/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008/0033027 A1 (BASCOMB, N et al.) 07 February 2008; abstract; paragraphs [0010], [0167]-[0168]	1-2, 3/1-2, 7
A	US 2016/0158198 A1 (VICUS THERAPEUTICS LLC) 09 June 2016; abstract; paragraphs [0010], [0018], [0021], [0033], [0158]	1-2, 3/1-2, 7
A	CA 2,082,310 A1 (JAMALI, F) 07 May 1994; page 5, second, third and fourth paragraphs; page 6, last paragraph; figures 2-3	1-2, 3/1-2, 7
A	US 2009/0238869 A1 (HEINICKE, G) 24 September 2009; abstract; paragraphs [0017], [0028]	1-2, 3/1-2, 7

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
05 December 2018 (05.12.2018)	21 DEC 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/59047

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-6, 8-30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.