In mice bearing sc M109 lung carcinoma efficacy can be dissociated from neurotoxicity

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ORAL ADMINISTRATION OF IXABEPILON

DESCRIPTION OF THE INVENTION

The compound ixabepilone has the structural formula,

![Structural Formula]


Ixabepilone has been approved by the US Food and Drug Administration for treatment of metastatic breast cancer, and is sold by Bristol-Myers Squibb Company (BMS) under the tradename IXEMPRA®. The approved product IXEMPRA® (ixabepilone) is administered via injection, and the active ingredient is sold in a product kit, together with a diluent. The recommended dosage of IXEMPRA is 40 mg/m² administered intravenously over 3 hours every 3 weeks.

Administration of ixabepilone under the current, IV has the potential for adverse side effects in patients, more particularly, such side effects may include peripheral neuropathy and/or myelosuppression, primarily neutropenia. These side effects can affect or limit the dose to be administered. It is currently recommended that when ixabepilone is administered to patients, that the patients be monitored for symptoms of neuropathy, primarily sensory, and for neutropenia with peripheral blood cell counts, and it is also recommended that these side effects be managed by dose adjustment(s) and delays.

Additionally, the current IV administration involves obvious drawbacks as compared, for example, with other forms of administration such as oral administration.
Oral administration of a capsule or tablet would offer advantages as compared with IV administration not limited to ease of use and accessibility. Oral administration of ixabepilone presents many issues, however. One such issue involves preparing a suitable formulation (e.g., tablet or capsule) for oral administration. Other issues relate to providing a suitable dose and/or regime for administration to achieve an optimal efficacious level of ixabepilone in patients while minimizing toxicity and managing side effects.

There is a need to provide a novel mode of administering ixabepilone that is more convenient than the current, IV administration (e.g., such as an oral form), that can achieve an efficacious level of ixabepilone in patients while minimizing and/or effectively managing side effects and/or minimizing the need for dose adjustments and delays.

BRIEF DESCRIPTION OF THE FIGURES

The invention is illustrated by reference to the accompanying drawings described below.

FIG. 1 shows the results of in vivo preclinical mice studies (in mice bearing sc M109 carcinoma) in which ixabepilone was administered and clinical neurotoxicity measured relative to efficacy (LCK) for administrations a) orally, every 4th days for 3 doses, as compared with b) the same dose administered via IV every 4 days, and c) the same dose administered via IV as a split dose;

FIG. 2 shows the results of in vivo preclinical mice studies (in mice bearing sc M5076 taxol resistant fibrosarcoma) in which tumor weight was measured as a function of days post-tumor implant for a control, as compared to a) taxol, and b) ixabepilone administered daily (10, QD); and c) ixabepilone administered as a split dose; and

FIG. 3 shows the results of in vivo preclinical mice studies (in mice bearing 16/C mammary carcinoma) in which tumor weight was measured as a function of days post-tumor implant for a control as compared with ixabepilone administered as a split dose (24 mpk, twice a day) and a daily dose (48 mpk, once daily).

DETAILED DESCRIPTION OF THE INVENTION
According to the present invention, novel uses of administering ixabepilone are provided that are more convenient and practical than IV administration and achieve a surprising efficacy to safety profile. In one embodiment, it has been surprisingly found that by administering ixabepilone orally under a split dose regime, and more particularly, following a dosing schedule wherein a dose (or herein, a “cycle dose”) of ixabepilone is orally administered as two or more daily unit dosages on an intermittent dosing cycle, surprisingly the efficacy is enhanced and/or side effects are substantially reduced. In one embodiment, the ixabepilone is administered as 3 oral unit dosages separated by six hours on Day 1 of an intermittent daily dosing cycle (e.g., in one embodiment, every 21 days), and an efficacious dose of ixabepilone is achieved, with substantially reduced risk of side effects such as neuropathy and/or neutropenia. More particular aspects of the invention are described further below.

The following are abbreviations of various terms that may be used herein.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the concentration-time curve</td>
</tr>
<tr>
<td>AUC(0-T)</td>
<td>area under the concentration-time curve from time zero to the time of the last quantifiable concentration</td>
</tr>
<tr>
<td>AUC(TAU)</td>
<td>area under the concentration-time curve in one dosing interval</td>
</tr>
<tr>
<td>BID</td>
<td>Twice-a day</td>
</tr>
<tr>
<td>BMS</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>C</td>
<td>Celsius</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>Cmax, CMAX</td>
<td>maximum observed concentration</td>
</tr>
<tr>
<td>Cmin, CMIN</td>
<td>trough observed concentration</td>
</tr>
<tr>
<td>CR</td>
<td>Complete Response</td>
</tr>
<tr>
<td>CV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cycle dose</td>
<td>Overall dose or drug administered at each intermittent dosing cycle. <em>E.g.</em>, cycle dose is 150 mg where 3 unit dosages of 50 mg are administered every 21 days.</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome p-450</td>
</tr>
<tr>
<td>D</td>
<td>Day</td>
</tr>
<tr>
<td>D/C</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Dl</td>
<td>Deciliter</td>
</tr>
<tr>
<td>DLT</td>
<td>Dose Limiting Toxicity</td>
</tr>
<tr>
<td>ER</td>
<td>Exposure Response</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>H</td>
<td>Hour</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
<tr>
<td>Intermittent dosing cycle</td>
<td>A cycle for administering dosages of drug, <em>e.g.</em>, preferably every 21 days. Other cycles are contemplated, <em>e.g.</em>, every week, every 10 days, every 2 weeks, every 18 days, etc.</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LCK</td>
<td>Log Cell Kill</td>
</tr>
<tr>
<td>LC</td>
<td>liquid chromatography</td>
</tr>
<tr>
<td>M</td>
<td>Meter</td>
</tr>
<tr>
<td>MDR</td>
<td>Multi-Drug Resistant</td>
</tr>
<tr>
<td>Mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>Min</td>
<td>Minute</td>
</tr>
<tr>
<td>MI</td>
<td>Milliliter</td>
</tr>
<tr>
<td>mpk</td>
<td>milligrams per kilogram</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>MTD</td>
<td>maximum tolerated dose</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>N</td>
<td>number of Subjects or observations</td>
</tr>
<tr>
<td>N/A</td>
<td>not applicable</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PO</td>
<td>Per Os (Oral)</td>
</tr>
<tr>
<td>Q</td>
<td>Every</td>
</tr>
</tbody>
</table>
ORAL ADMINISTRATION OF IXABEPILONE AND INVENTIVE DOSING SCHEDULES

According to one embodiment of the invention, there is provided use of ixabepilone in the manufacture of a medicament for treating cancer in a human patient, wherein said medicament is orally administered to said human patient according to a split daily dose administered on an intermittent dosing cycle. The cycle dose, or amount of ixabepilone administered at each cycle, is administered according to a “split” daily unit dose, \textit{i.e.}, of two or more administrations separated by one or more hours on Day 1 of the cycle, and then again at each Day of the cycle at which drug is to be administered. Preferably, the split doses are separated by a period of time from 3 to 12 hours, more preferably, from 4 to 8 hours, and most preferably by 6 hours. For example, the cycle dose can be split into two, three or four unit daily dosages, or more preferably, into three unit daily dosages, separately by 4 to 8 hours each. In the embodiment where three unit daily dosages are used, they can be separated by 6 hours on Day 1 of an intermittent dosing cycle, and then again, the same dose and cycle can be applied on the next Day of drug administration. Each unit dosage is independently selected from 10-60 mg of ixabepilone (more preferably 20-50 mg ixabepilone), and the dosing cycle is selected from 10, 15, and 21 day cycles, more preferably from a 21 day cycle.

For example, in one embodiment, human patients are administered a cycle dose of ixabepilone of 150 mg, administered orally. The patients are suffering from cancer, typically breast, prostate, small cell lung, or renal cancer. On Day 1, patients receive 3
unit dosages of 50 mg each; the administration of each unit dose is separated by 6 hours; and the intermittent dosing cycle is 21 days. Thus, the patients in this embodiment receive 150 mg every 21 days, with the 150 mg being administered as three unit doses of 50 mg separated by 6 hours on Day 1, then every 21 days. A surprisingly advantageous safety-to-efficacy profile is achieved. The ixabepilone is highly efficacious in treating the cancer, and there are reduced manifestations of side effects, as compared with patient populations having received 40 mg/m² administered intravenously over 3 hours every 3 weeks. Side effects that are effectively managed and/or may be surprisingly reduced with the oral administration according to the split dose may include, without limitation, neuropathy, neutropenia, fatigue/asthenia, myalgia/arthritis, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, musculoskeletal pain, palmar-plantar erythrodysesthesia syndrome, anorexia, abdominal pain, nail disorder, constipation, leukopenia, anemia, and/or thrombocytopenia.

According to one embodiment of the invention, there is provided use of ixabepilone as stated above, or otherwise herein, wherein the unit dosage administered 3 times on Day 1 of the intermittent dosing cycle is selected from 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg of ixabepilone, and/or 5 mg increments therebetween. The amount of ixabepilone selected for each unit dosage can be variably selected to achieve the overall desired, cycle dose. However, preferably, the ixabepilone is administered wherein the cycle dose is 145-155 mg, more preferably 150 mg, and the unit dosage is at each administration 45 to 55 (more preferably at 50 mg).

According to one embodiment of the invention, there is provided use of ixabepilone as stated above, or otherwise herein, wherein the unit dosage is administered as at least a split dose on Day 1 of the intermittent dosing cycle and wherein the overall cycle dose is selected from 100 to 160 mg, more preferably 120 to 155 mg, even more preferably 140-155 mg, and most preferably 150 mg.

Various dosing cycles may be selected to administer the split dose. A shorter cycle may be selected with a reduction in the overall cycle dose. For example, dosing cycles may be every 7, 10, 15, 18 or 21 days. Preferably, a 21 day cycle is applied.

According to one embodiment of the invention, there is provided use of an oral unit dosage of ixabepilone, in the manufacture of a medicament for treatment of cancer,
in which such treatment comprises a combination with a unit dosage of one or more inhibitors of CYP3A4/5 enzymes, for concurrent or sequential use, in any order.

The invention will now be further illustrated with reference to the below Examples which are intended to be illustrative and non-limiting in nature.

EXAMPLES 1-3: PRECLINICAL DATA ON SPLIT DOSING OF IXABEPILON

Example 1

Preclinical studies were performed to evaluate the effects of oral dosing regimes for administering ixabepilone as compared with IV administration. For example, Figure 1 shows the results of in vivo preclinical mice studies (in mice bearing sc M109 carcinoma) in which ixabepilone was administered and clinical neurotoxicity measured relative to efficacy (LCK) for administrations performed (a) orally, every 4th days for 3 doses, as compared with (b) the same dose administered via IV every 4 days, and (c) the same dose administered via IV as a split dose.

The data shows the split dose regime, as compared with a single large dose, is surprisingly advantageous in reducing neurotoxicity and achieving an advantageous efficacy/safety profile. The BID regime even when administered IV produced greater absolute efficacy overall (>2 LCK). When comparing the two regimes at the same neurotoxicity level (e.g. clinical grade 1), the split dose regime consistently produced superior antitumor activity. This remarkable improvement in efficacy/safety profile may be a consequence of an improved pharmacokinetics profile.

Additionally, the oral administration as described herein involves an improved formulation with favorable pharmacokinetics and/or tissue distribution profiles. Further, as seen on Figure 1, the oral administration demonstrated an improved safety/efficacy profile as compared with the IV administration.

Example 2

FIG. 2 shows the results of in vivo preclinical mice studies (in mice bearing sc M5076 taxol resistant fibrosarcoma) in which tumor growth was measured as a function of days post-tumor implant for a control group, as compared to a) taxol, and b) ixabepilone administered as a single dose per day every 4 days for 3 doses (10 mpk, Q4Dx3, IV); and
c) ixabepilone administered as a twice per day split dose 6 hours apart (5 mpk, BID, Q4Dx3, IV). As can be seen, the split dosing of oral ixabepilone produced surprisingly advantageous efficacy results.

Example 3

FIG. 3 shows the results of in vivo preclinical mice studies (in mice bearing 16/C mammary carcinoma) in which tumor weight was measured as a function of days post-tumor implant for a control as compared to ixabepilone administered orally as a split dose (24 mpk, twice-a-day) and orally once-a-day dose (48 mpk, once daily). As can be seen, the oral split dose demonstrated surprisingly superior activity in controlling tumor growth, i.e., showing complete tumor growth inhibition for over 60 days post tumor implant.

EXAMPLE 4: Modeling and Simulation of Clinical Results

Existing population PK and exposure-response (E-R) models for ixabepilone administered via IV were extended to describe E-R following oral administration of ixabepilone, and the potential benefit-risk of alternative oral schedules were examined by clinical trial simulation. The total oral dose over 3 weeks was selected to be equivalent to that of an IV dosage regime of a single 70 mg dose every 3 weeks, by taking oral bioavailability into account. The potential benefit of a number of schedules was assessed by the total time for which the plasma concentration of ixabepilone was above a pre-specified threshold (based on in vivo pharmacology data), and the risk was assessed by the severity of neutropenia. An existing population PK (PPK) model for ixabepilone given via IV was extended by including an oral absorption component in the model, to estimate oral bioavailability and describe plasma concentration-time profiles of ixabepilone following oral administration and predict the time above the threshold concentration. The extended PPK model was coupled with an existing ER model for neutropenia, that had also been developed with data following IV administration of ixabepilone, and this ER model was used to assess the incidence and severity of neutropenia for a number of alternative oral schedules. From this modeling and simulation of clinical trial results, a schedule of 3 doses given every 6 hours was
discovered to have the least risk of neutropenia and the greatest potential for enhanced efficacy.

EXAMPLE 5: Clinical Trial

Ixabepilone is orally administered every 21 days in human patients with advanced cancer (e.g., breast, renal, small cell lung, and/or prostate cancer). The starting dose level is a 30 mg/dose for ixabepilone given as 3 oral doses separated by 6 hours on day 1 of a 21-dosing cycle.

The starting dose may be adjusted in 10 mg increments to cohorts of patients. Dose escalation levels are defined in the following table:

<table>
<thead>
<tr>
<th>Dose Level Cohort</th>
<th>1xabepilone (mg for each of 3 doses) D1 of a 21-Day Cycle</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort -1a</td>
<td>10 mg/dose</td>
<td>3 – 6</td>
</tr>
<tr>
<td>Cohort 1b</td>
<td>20 mg/dose</td>
<td>3 – 6</td>
</tr>
<tr>
<td>Cohort 1 (start)</td>
<td>30 mg/dose</td>
<td>3 – 6</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>40 mg/dose</td>
<td>3 – 6</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>50 mg/dose</td>
<td>3 – 6</td>
</tr>
<tr>
<td>Subsequent cohorts</td>
<td>Increase 10 mg/dose</td>
<td></td>
</tr>
</tbody>
</table>

Initially at least 3 patients are treated at each dose level.

- Where none of the 3 patients experience a DLT, then the next cohort of subjects are enrolled at the next higher dose level.

- Where 1 of the 3 subjects experience a DLT, up to 3 additional subjects are enrolled at that dose level. If no additional subjects experience a DLT, then the next cohort of subjects are enrolled at the next higher dose level.
Where 2 or more subjects out of 6 (or ≥ 33% of a cohort larger than 6) experience a DLT, then the next cohort of subjects is enrolled at the next lower dose level in order to reach a total of 6 subjects at that dose level.

The definition for DLT is an adverse event considered related to ixabepilone and occurring during the first cycle of drug administration, including: Grade 4 neutropenia for ≥ 5 consecutive days or febrile neutropenia with or without sepsis with an ANC < 1000 cells/mm³; Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding requiring platelet transfusion; Grade 3 or 4 nausea, vomiting, or diarrhea; any other ≥ Grade 3 non-hematologic toxicity excluding those that are not clinically significant (e.g., transient arthralgia/myalgia). Delayed recovery (to Grade ≤ 1 or baseline, except for alopecia) from a toxicity related to treatment with ixabepilone, which delays the initiation of Cycle 2 by 3 weeks or more.

The MTD will be based on Cycle 1 data and is the maximum dose which can be given to 6 subjects such that not more than 1 subject experiences a DLT (or < one-third if there are more than 6 treated subjects).

PK samples are obtained during Cycle 1.

Accordingly, three human patients suffering from cancer are orally administered ixabepilone as 3 oral unit dosages of 30 mg, separated by 6 hours on Day 1 every 21 days; advantageous results are achieved, and three human patients suffering from cancer are orally administered ixabepilone as 3 oral unit dosages of 40 mg, separated by 6 hours on Day 1 every 21 days; again, advantageous results are achieved and six human patients suffering from cancer are orally administered ixabepilone as 3 oral unit dosages of 50 mg, separated by 6 hours on Day 1 every 21 days. Additional clinical trials and data evaluation is on-going.

Surprisingly, a remarkable efficacy to safety profile is achieved with the oral administration, which is more convenient than the IV administration of 40 mg/m² administered intravenously over 3 hours every 3 weeks. In one embodiment, surprisingly, efficacious results are achieved with manageable levels of, and/or
substantially reduced incidence of, side effects such as, for example, neuropathy and neutropenia. Other potential adverse reactions are also effectively managed and/or surprisingly reduced, such as fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, musculoskeletal pain, palmar-plantar erythrodysesthesia syndrome, anorexia, abdominal pain, nail disorder, constipation, leukopenia, anemia, and/or thrombocytopenia.

**UTILITY**

Ixabepilone is useful as a microtubule-stabilizing agent. Ixabepilone is useful in the treatment of a variety of cancers and other proliferative diseases including, but not limited to, the following:

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid, and skin, including squamous cell carcinoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;
- tumors of mesenchymal origin, including fibrosarcoma, rhabdomyoscaroma, and osteosarcoma; and
- other tumors, including melanoma, xeroderma pigmentosum, keratoacanthoma, seminoma, thyroid follicular cancer, and teratocarcinoma.

In a preferred embodiment, ixabepilone and the methods of administration described herein are used to treat human patients diagnosed with renal, prostate, and/or breast cancer.

Ixabepilone is useful for treating patients who have been previously treated for cancer, as well as those who have not previously been treated for cancer. The methods and compositions of this invention, including the enteric coated beads, can be used in first-line and second-line cancer treatments and for treating refractory or resistant cancers.

Ixabepilone will inhibit angiogenesis, thereby affecting the growth of tumors and providing treatment of tumors and tumor-related disorders. Such anti-angiogenesis
properties will also be useful in the treatment of other conditions responsive to anti-
angiogenesis agents including, but not limited to, certain forms of blindness related to
retinal vascularization, arthritis, especially inflammatory arthritis, multiple sclerosis,
restinosis, and psoriasis.

Ixabepilone will induce or inhibit apoptosis, a physiological cell death process
critical for normal development and homeostasis. Alterations of apoptotic pathways
contribute to the pathogenesis of a variety of human diseases. The subject compounds, as
modulators of apoptosis, will be useful in the treatment of a variety of human diseases
with aberrations in apoptosis including, but not limited to, cancer and precancerous
lesions, immune response related diseases, viral infections, kidney disease, and
degenerative diseases of the musculoskeletal system.

The ixabepilone may also be formulated or co-administered with other
therapeutic agents that are selected for their particular usefulness in administering
therapies associated with the aforementioned conditions. Ixabepilone may be formulated
with agents to prevent nausea, hypersensitivity, and gastric irritation, such as anti-
emetics, and H₁ and H₂ antihistamines. The above therapeutic agents, when employed in
combination with ixabepilone, may be used in those amounts indicated in the Physicians’
Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

More particularly, according to one embodiment of the invention, there is
provided use of a oral unit dosage of ixabepilone, in the manufacture of a medicament for
treatment of cancer, in which such treatment comprises a combination with a unit dosage
of one or more inhibitors of CYP3A4/5 enzymes, for concurrent or sequential use, in any
order. It is contemplated that this combination may provide particular advantages than
obtainable with the unit dosage of ixabepilone, or unit dosage of CYP3A4/5 inhibitor,
alone.

Cytochrome P450 enzymes include a number of human cytochrome P450
enzymes, including the CYP3A family of enzymes, i.e., CYP3A4 and CYP3A5.
References to “CYP3A4/5” are intended to include either or both of CYP3A4 and
CYP3A5. This family of enzymes catalyzes oxidative and reductive reactions and has
activity towards a chemically diverse group of substrates. These enzymes are the major
catalysts of drug biotransformation reactions and also serve an important detoxification
role in the body. Inhibitors of the cytochrome P450 enzymes, particularly, CYP3A4/5
inhibitors, interfere with the body's ability to detoxify. Thus, developing pharmaceuticals
for human consumption that inhibit CYP3A4/5, and/or that may effectively and safely be
used in combination with compounds that inhibit CYP3A4/5, presents particular
challenges. See, for example, the Guidance for Industry: In Vivo Drug Metabolism/Drug
Interaction Studies--Study Design, Data Analysis, and Recommendations for Dosing and
Labeling prepared by the Food and Drug Administration (November 1999). In research
and development of pharmaceuticals, CYP3A4/5 inhibition may be considered an
undesirable activity, and efforts are directed in research to develop compound that do not
derivatives and methods of their use.”

Commonly-known CYP3A4/5 inhibitors include HIV protease inhibitors
(indinavir, nelfinavir, ritonavir), amiodarone, cimetidine, clarithromycin, diltiazem,
erthromycin, fluvoxamine, grapefruit juice, itraconazole, ketoconazole, mibebradil,
nefazodone, troleandomycin, and verapamil. Lapatinib, an FDA approved tyrosine
kinase inhibitor available from Glaxosmith Kline, is also a CYP3A4/5 inhibitor. Thus,
the term CYP3A4/5 inhibitors as used herein include each of these substances, as well as
any other CYP3A4/5 inhibitors well known in the field. See, e.g., WO 2005/007631.
Potent CYP3A4/5 inhibitors, which are of particular interest in view of their potency,
include ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, nelfinavir,
delavirdine, and voriconazole.

Ketoconazole, one of the potent CYP3A4/5 inhibitors, is an imidazole compound
used as an antifungal agent. Ketoconazole is cis-1-acetyl-4-[4-[2-(2,4-di-chlorophenyl)-
2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine, and has the
structure:
Ketoconazole was originally described in US Pat. 4,335,125, incorporated herein, with its principal utility being as an antifungal agent. Ketoconazole and formulations are well known and widely described, for example, see US Pat. 4,569,935; US 2005/0013834 A1, “Pharmaceutical Formulations Comprising Ketoconazole”; US 2004/0063722 A1, “Antifungal Ketoconazole Composition for Topical Use”; Rotstein et al., J. Med Chem. (1992) 35, 2818-2825 (describing stereoisomers of ketoconazole).

Applicant herein has discovered that a combination of orally-administered ixabepilone with CYP3A4/5 inhibitors provides surprisingly advantageous results.

PREPARATION OF TABLET OR CAPSULE OF Ixabepilone


Preparation of the Tablets and/or Capsules for Oral Administration

The preparation of tablets and/or capsules of ixabepilone is described in WO2006/055740 A1 (US application Serial No.11/281,855), titled “Enteric Coated Bead Comprising Ixabepilone, and Preparation thereof”, which published on 26 May 2006. In carrying out the present invention, an enteric coated bead comprising ixabepilone may be used to orally administer ixabepilone to a patient. The enteric coated bead may comprise a coated particle, wherein the active ingredient ixabepilone is encapsulated by an enteric coating. The enteric coating is capable of protecting the ixabepilone, which is susceptible to degradation, decomposition, or deactivation during exposure to acidic conditions, from low pH gastric fluids typically encountered during passage through the stomach into the intestine. The enteric coating is capable of minimizing or preventing exposure of the active ingredient layer to stomach acid. This prevents ixabepilone from being released in the stomach or the stomach acid from penetrating through to the active ingredient layer.

Upon passage of the enteric coated bead to the small intestine, the enteric coating
partially or completely dissolves in the higher pH conditions encountered in the intestine, leading to the release of ixabepilone, and its passage to the bloodstream of the patient.

The enteric coated bead may comprise a coated particle encapsulated by an enteric coating. The coated particle may comprise a monolithic particle of ixabepilone, ixabepilone mixed with other inert or active ingredients, and/or a base particle, which may provide a seed particle for the application of an active ingredient layer. When a base particle is used, the base particle may comprise a pharmaceutically acceptable material that is capable of carrying the active ingredient layer. Generally, the base particle may comprise, for example, a pharmaceutically inert material, such as, for example, sugar, starch, microcrystalline cellulose, lactose, or combinations thereof. Optionally, the base particle may further comprise one or more active agents. The shape of the base particle is typically spherical or semispherical, although other shapes are contemplated. Average diameters for the base particles are typically, for example, in the range of from about 0.1 millimeters to about 5 millimeters. Examples of suitable base particles include Nu-Pareil™ Sugar Spheres NF (Chr. Hansen, Inc., WI) and Celphere™ microcrystalline cellulose spheres (Asahi Kasei Kogyo Kabushiki Kaisha Corp., Japan). Typically, the enteric coated bead may comprise, for example, from about 10 to about 80 weight % base particle, preferably from about 15 to about 70 weight % base particle, and more preferably from about 20 to about 65 weight % base particle, based on the weight of the enteric coated bead. Preferably, the base particle is substantially free of moisture. More preferably, the base particle may comprise less than 3 weight % water, based on the weight of base particle.

The coated particle may comprise a monolithic particle or a multiple-component particle, e.g., wherein an active ingredient layer is disposed around the base particle. The active ingredient layer may be applied to the base particle and may form a surface layer on the surface of the base particle, absorb into the base particle, or a combination thereof. The active ingredient layer may be completely or partially distributed on, in, and/or beneath the surface of the base particle. Preferred is an active ingredient layer that is uniformly disposed on the surface of the base particle.

The active ingredient layer may comprise ixabepilone, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof. In addition to ixabepilone, the active
ingredient layer may optionally comprise at least one additional active agent, such as an anticancer drug. In one embodiment, the active ingredient may comprise a mixture of ixabepilone and a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug of ixabepilone. For example, the active ingredient layer may comprise a mixture of ixabepilone and a clathrate of ixabepilone. Suitable levels of ixabepilone include, for example, those in the range of from about 0.1 weight % to about 10 weight %, preferably from about 0.2 weight % to about 5 weight %, and more preferably from about 0.5 weight % to about 4 weight %, based on the weight of the enteric coated bead.

The ixabepilone used in the tablet or capsule preferably are particles having a particle size of D50 =~4.5um to 7.5um (um=microns), more preferably ~5 to 6um, and even more preferably 5um, and a D90 =~18.5 um to ~44um, more preferably 19 to 25 ~um, and most preferably 20um. In other embodiments, the ixabepilone particles as used in the oral tablets or capsules have sizes as shown below:

<table>
<thead>
<tr>
<th>Particle Size</th>
<th>Particle Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>D50 (microns)</td>
<td>D90 (microns)</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
</tr>
</tbody>
</table>

The D50 value refers to a parameter for a population of particles in which 50% of the particles have diameters less than the D50 value and 50% of the particles have diameters greater than the D50 value, based on volume distribution. The D90 value refers to a parameter representing the minimum value at which 90% of the particles have diameters less than the D90 value. The D50 and the D90 values may be determined by a suitable static laser light scattering technique, such as by measurement with the Horiba™ LA-910 Laser Diffraction Particle Size Analyzer (Horiba, Ltd., Japan). As used herein “average particle diameter” refers to the D50 value. Optical microscopy may be employed to verify the absence of large agglomerates.
The active ingredient layer also may comprise binder. The binder may be employed to improve adhesion of ixabepilone to the base particle and/or to provide cohesion of the active ingredient layer. Materials suitable as binders include, for example, starch; gelatin; sugars such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums such as acacia, sodium alginate, methyl cellulose, carboxymethylcellulose, and polyvinylpyrrolidone (PVP) polymers and copolymers such as polyvinylpyrrolidone/polyvinyl acetate (PVP-PVA) copolymers; cellulosics such as ethyl cellulose, hydroxypropyl cellulose, or hydroxypropyl methylcellulose; polyethylene glycol; and waxes. For example, suitable commercially available materials include Avicel™ PH 101, Avicel™ RC 591, and Avicel™ CL 611 cellulose crystallite materials, (FMC Corp., PA). One or more different binders may be used in the active ingredient layer. One or more optional ingredients that may be included in the active ingredient layer are, for example, buffers, antifoam agents, and plasticizers. The enteric coated bead may comprise, for example, from about 2 to about 80 weight % of the active ingredient layer, preferably from about 10 to about 70 weight % of the active ingredient layer, and more preferably from about 20 to about 60 weight % of the active ingredient layer, based on the weight of the enteric coated bead. Preferably, the active ingredient layer is substantially free of moisture.

The tablet or capsule of ixabepilone preferably has an enteric coating that encapsulates the active ingredient. The enteric coating is insoluble or has low solubility in acid solutions characteristic of gastric fluids encountered in the stomach, such pH values of less than about 3. At higher pH values, such as those encountered in the small intestine, the enteric coating dissolves to allow the release of ixabepilone. Examples of the higher pH values encountered in the small intestine include pH values of greater than about 4.5, preferably pH values of greater than about 5, and most preferably pH values in the range of from about 5 to about 7.2.

Suitable materials for forming the enteric coating, include, for example, enteric coating polymers, such as, for example, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, acrylic acid copolymers, hydroxypropyl methylcellulose acetate succinate, and methacrylic acid copolymers. One example of a suitable methacrylic acid copolymer is Eudragit™ L-30-D 55 aqueous
copolymer dispersion, which may comprise an anionic copolymer derived from
methacrylic acid and ethyl acrylate with a ratio of free carboxyl groups to the ethyl ester
groups of approximately 1:1, and a mean molecular weight of approximately 250,000,
and is supplied as an aqueous dispersion containing 30 weight % solids. Eudragit™ L-
30-D 55 aqueous copolymer dispersion is supplied by Röhm-Pharma Co., Germany.
The enteric coated bead may comprise, for example, from about 5 to about 55 weight %
of the enteric coating, preferably from about 10 to about 45 weight % of the enteric
coating, and more preferably from about 15 to about 40 weight % of the enteric coating,
based on the weight of the enteric coated bead. Preferably, the enteric coating is
substantially free of moisture.

The enteric coating optionally comprises other materials, such as plasticizers,
colorants, antifoam agents, and anti-adherents.

The enteric coated bead may optionally comprise one or more subcoat layers
that are situated between the base particle and the active ingredient layer, or the active
ingredient layer and the enteric coating. A subcoat layer may be employed to minimize
contact between ixabepilone contained in the active ingredient layer and an enteric
coating comprising acid groups, such as methacrylic acid copolymer. For example, the
enteric coated bead may comprise from about 0.1 to about 10 weight % of the subcoat
layer, preferably from about 0.5 to about 5 weight % of the subcoat layer, and more
preferably from about 2 to about 4 weight % of a subcoat layer, based on the weight of
the enteric coated bead. Suitable materials to form the subcoat layer include starch;
gelatin; sugars such as sucrose, glucose, dextrose, molasses, and lactose; natural and
synthetic gums such as acacia, sodium alginate, methyl cellulose,
carboxymethylcellulose, and polyvinylpyrrolidone (PVP) polymers and copolymers such
as PVP-PVA copolymers; celluloses such as ethylcellulose, hydroxypropyl cellulose, and
hydroxypropyl methyl cellulose; polyethylene glycol, and waxes. The subcoat layer may
further comprise one or more plasticizers, such as polyethylene glycol, propylene glycol,
triethyl citrate, triacitin, diethyl phthalate, tributyl sebacate, or combinations thereof.

In one embodiment, the enteric coated bead may optionally comprise a
subcoat layer interposed between the active ingredient layer and the enteric coating. In
this embodiment, the enteric coated bead may comprise from about 0.1 to about 10
weight % of the subcoat layer, preferably from about 0.5 to about 5 weight % of the subcoat layer, and more preferably from about 2 to about 4 weight % of a subcoat layer, based on the weight of the enteric coated bead. Preferably, the subcoat layer is substantially free of moisture.

The enteric coated bead optionally comprises other materials such as flavoring agents, preservatives, or coloring agents as may be necessary or desired.

In one non-limiting embodiment, the enteric coated bead is substantially free of moisture. By “substantially free of moisture,” it is meant that the enteric coated bead comprises less than about 4 weight % water, preferably less than about 3 weight % water, and more preferably, less than about 2 weight % water, based on the weight of the enteric coated bead.

The enteric coated bead may be contacted with a hydrophobic material such as talc, magnesium stearate, or fumed silica to form a hydrophobic layer on the surface of the enteric coated bead. The hydrophobic layer is useful to reduce agglomeration of the individual enteric coated beads and/or to reduce static during the handling of the enteric coated beads.

The enteric coated beads of ixabepilone for use with this invention may be prepared by a process that reduces the exposure of ixabepilone to moisture, heat, or a combination of moisture and heat. Such a process ensures high potency and good uniformity of the active pharmaceutical agent, since ixabepilone is susceptible to degradation or decomposition in the presence of water, and especially a combination of moisture and heat.

A process for preparing the enteric coated bead for a capsule or tablet may comprise:

a) providing base particles;

b) applying an active ingredient mixture and binder to the base particles, wherein the active ingredient mixture may comprise:

i) ixabepilone, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof, and

ii) solvent, water, or a mixture thereof;

c) drying the base particles having application of the active ingredient mixture to provide coated particles; and

d) applying enteric coating to the coated particles to provide the enteric coated beads.
In processes to prepare the enteric coated bead for use with this invention, the active ingredient mixture may also comprise the binder, thus allowing co-application of a single mixture. Alternatively, the active ingredient mixture and a solution comprising the binder may be premixed immediately prior to application.

The active ingredient mixture may comprise ixabepilone in solvent, water, or a mixture thereof. The active ingredient mixture may be a solution comprising ixabepilone dissolved in the solvent, water, or mixture thereof. Alternatively, the active ingredient mixture may be an active agent suspension comprising particles of ixabepilone dispersed in the solvent, water, or mixture thereof. Suitable solvents include, for example, alcohols such as methanol, ethanol, n-propanol, and isopropanol; and acetone. The active ingredient mixture may be prepared by admixing ixabepilone in solvent, water, or a mixture thereof. Optionally, the binder may be included in the active ingredient mixture. Ixabepilone and the optional binder may be combined in any order with the solvent, water, or mixture thereof. Typically, mixing is required to minimize any localized concentrations of ixabepilone or the optional binder in the solvent, water, or mixture thereof. Mixing may be provided by a mechanical device, such as a magnetic or overhead stirrer.

In one embodiment, the enteric coated bead for use with this invention is prepared by applying an active ingredient suspension and binder to the base particles. Preferably, the active ingredient suspension is an aqueous active ingredient suspension comprising the particles of ixabepilone dispersed in an aqueous medium. The aqueous medium may comprise greater than about 50 weight % water and optionally, one or more water miscible solvents, based on the weight of the aqueous medium. Preferably the aqueous medium may comprise at least about 65 weight % water, more preferably at least about 75 weight % water, and most preferably at least about 85 weight % water, based on the weight of the aqueous medium. The aqueous suspension of the ixabepilone particles provides a reduction in contact between the aqueous medium and ixabepilone, compared to a solution of ixabepilone, and thus decreases the rate of degradation or decomposition of ixabepilone. The aqueous active ingredient suspension may be prepared by admixing ixabepilone particles and optionally, the binder, in water and optionally, water miscible solvent. The ixabepilone particles and the optional binder may be combined with the
water and/or the optional water miscible solvent in any order. Typically, mixing is
required to disperse the ixabepilone particles and minimize any localized concentrations
of the ixabepilone particles or the optional binder. Suitable size ranges for the
ixabepilone particles include, for example, from less than about 1000 microns, preferably
less than about 500 microns, and more preferably less than about 250 microns. The
ixabepilone particles may be amorphous or crystalline. Preferably, the ixabepilone
particles are crystalline. Examples of crystalline forms of ixabepilone, such as Form A
and Form B, are disclosed in U.S. Patent 6,689,802. The active ingredient suspension
may comprise from about 1 to about 50 weight % ixabepilone particles, preferably from
about 2 to about 30 weight % ixabepilone particles, and more preferably from about 3 to
about 20 weight % ixabepilone particles, based on the weight of the active ingredient
suspension. Preferably, the active ingredient suspension has a pH in the range of from
about 6 to about 9, more preferably in the range of from about 6.5 to about 8, and most
preferably in the range of from about 6.5 to about 7.5. The active ingredient suspension
may optionally comprise other ingredients, such as buffers; dispersing agents such as
surfactants or low molecular weight polymers; antifoaming agents, and pH adjusting
agents such as acids and bases.

The binder may be provided as a solution or dispersion in water.

In one embodiment, the active ingredient mixture may comprise, for example, from about
1 to about 30 weight % of the at least one binder, preferably from about 2 to about 20
weight % of the at least one binder, and more preferably from about 3 to about 10 weight
% of the at least one binder, based on the weight of the active ingredient mixture.
The active ingredient mixture and the binder solution may be applied to the base particles
as a spray or a stream while base particles are in motion. The conditions are preferably
controlled to minimize particle agglomeration of the base particles. Subsequently, the
solvent and/or water is removed from the applied active ingredient mixture leaving the
coated particles having the active ingredient layer disposed on the base particle.

The enteric coating may be applied to the coated particles by applying a
mixture of the enteric coating as a spray or stream while the coated particles are in
motion. The enteric coating mixture may be a solution or a suspension. The conditions
are preferably controlled to minimize particle agglomeration. The enteric coating
mixture may comprise the enteric coating material in an aqueous or nonaqueous solvent or mixture thereof. Suitable solvents include, for example, alcohols such as methanol and isopropanol; and acetone. Mixtures of solvents or mixtures of water and one or more water miscible solvents may be used. The enteric coating material may be dissolved into the solvent to provide a solution, or alternatively, may be a dispersion of particles, to provide a suspension, such as an aqueous copolymer dispersion. Typically, the enteric coating mixture may comprise, for example, from about 5 to about 50 weight % of the enteric coating material, and preferably from about 10 to about 40 weight % of the enteric coating material, based on the weight of the enteric coating mixture.

Drying to remove the solvent and/or water may be applied during and/or after application of the enteric coating mixture. In one embodiment, the drying conditions include an inlet drying air temperature in the range of from about 20°C to about 70°C, an inlet air humidity of less than about 50% relative humidity, a product bed temperature in the range of from about 20°C to about 40°C, and air flow that is sufficient to remove the free water vapor.

A fluid bed spraying apparatus, a tangential spray coater, or a rotating pan type coater may be employed to spray the active agent suspension onto the base particles, and/or to spray the enteric coating mixture onto the coated particle.

A fluid bed coater is an apparatus that can fluidize particles such as beads while simultaneously spraying on and drying a film coat. The fluidizing air is heated to the desired temperature and the air flow adjusted to the flow rate for proper fluidization and drying. A pan coater is an apparatus in which particles are tumbled in a pan while spraying a film coat. Simultaneously air of the proper temperature and airflow passes through the bed of particles to dry the applied film coat.

One aspect of the invention comprises orally administering a capsule comprising a multitude of the enteric coated beads. The capsule may be prepared by filling a capsule shell, such as a gelatin capsule shell, with the enteric coated beads. The capsule allows for easier swallowing during oral administration of the enteric coated beads. Optionally, the capsule may comprise at least one hydrophobic material to reduce agglomeration of the individual enteric coated beads in the capsule and/or to reduce static during the loading of the enteric coated beads into the capsule. Generally, the amount of
the optional hydrophobic material is preferably kept to a level where it is just enough to prevent particle sticking after the capsule shell has dissolved, but not too much to retard dissolution. Examples of suitable hydrophobic materials include talc, magnesium stearate, stearic acid, glyceryl behenate, hydrogenated cottonseed oil, trirmyristin, tripalmitin, tristearin, and fumed silica. Examples of commercially available hydrophobic materials include LubriTal™ additive (Penwest Pharmaceutical Co., NJ); Dynasan™ 114, Dynasan™ 116, and Dynasan™ 118 additives (Sasol North America, TX); and Compritol™ 888 ATO additive (Gattefosse Co., France). A preferred hydrophobic material is talc.

Below are some specific examples for making the enteric coated beads of ixabepilone that may be used in the present invention methods and Uses.

**Tablet/Capsule Preparation Example 1**

An active ingredient suspension was prepared containing ixabepilone. First, 2.783 g Tris powder (tris(hydroxymethyl aminomethane)), 500 ml water, and 1 N HCl were mixed to provide a 0.046 M Tris buffer solution having a pH of 8.1. Next, a mixture of 43.5 g Tris buffer solution (43.5 g) and 2.5 g Opadry™ Clear Coat powder (Colorcon, Inc., PA), as the binder, was prepared. To this mixture, 4 g of ixabepilone, as crystals, was added and stirred for approximately 30 minutes to provide the active ingredient suspension. The active ingredient suspension was passed through a 60 mesh screen to remove any agglomerates.

**Preparation of Coated Particles**

The coated particles were prepared by applying the active ingredient suspension onto base particles. The base particles were 18/20 mesh sugar beads, (Sugar Spheres, NF particles, (Chr. Hansen, Inc., WI)) having particle diameters of greater than 0.85 mm and less than 1 mm.

The active ingredient suspension was applied to the base particles by spraying using a fluid bed processor that was set up as a Wuster spray coating system. The spray coating system included an Aeromatic-Fielder MP-MICRO™ fluid bed processor (Niro Inc., Maryland) equipped with a 0.8 mm spray tip. The fluid bed processor was charged
with 90 g of the sugar beads and then preheated to approximately 50°C for several minutes.

The active ingredient suspension was applied to the base particles with the following application and drying parameters: a spray rate of 1.1 g/minute with a spray atomization pressure of 1.8 bar (180 kilopascals), an inlet temperature of 68 °C, an outlet temperature of 32°C, a product bed temperature of 32°C, and a fan speed of 4 m³/hr. During the application process, the active ingredient suspension was slowly stirred. After application of the active ingredient suspension was completed, the inlet temperature was maintained at the final inlet temperature until the bed product temperature reached 40°C.

The resulting coated particles contained 2.75 weight % of ixabepilone, based on the weight of the coated particle.

Application of Subcoat Layer

A subcoat can be applied to the coated particles. The subcoat solution can be prepared by combining 5 g Opadry™ Clear Coat powder and 95 g water and stirring until a clear solution was obtained.

In the subcoating procedure, the fluid bed processor used to prepare the coated particles was employed. The fluid bed processor, which contained 80 g of the coated particles, was preheated to approximately 50°C for several minutes. The subcoat layer was applied using the application and drying parameters disclosed hereinabove to the preparation of the coated particles. During the application process, the subcoated solution was slowly stirred. After application of the subcoat solution was completed, the inlet temperature was maintained at the final inlet temperature until the bed product temperature reached 40 °C. The resulting coated particles, which had a subcoat, contained approximately 2 weight % subcoat, based on the total weight of the resulting coated particles.

Application of Enteric Coating

An enteric coating was applied onto the coated particles having a subcoat. The enteric coating solution was prepared by first filtering Eudragit™ L30D55 polymer dispersion (Röhm GmbH and Co., Darmstadt, Germany) through a 60 mesh screen. Eudragit™ L30D55 polymer dispersion is an aqueous suspension containing methacrylic acid copolymer. The filtered Eudragit polymer dispersion (200g) was diluted with 89.5 g
water. Next, 9 g diethyl phthalate was added to the diluted Eudragit polymer dispersion, followed by the addition of 9.5 g of 1 N NaOH solution. The pH of the resulting enteric coating solution was 5.0±0.1.

In the enteric film coating procedure, the fluid bed processor used to prepare the coated particles was employed. The fluid bed processor, which contained 70 g of the coated particles, was preheated to approximately 50°C for several minutes. The enteric coating solution was applied using the following application and drying parameters: 0.8 mm spray tip, 1.1 g/minute spray rate, spray atomization pressure was 1.8 bar, inlet temperature 65°C, outlet temperature 30°C, product bed temperature 30°C, and fan speed of 3.5 m³/hr. During the application process, the enteric coating solution was slowly stirred. After application of the enteric coating solution was completed, the inlet temperature was maintained at the final inlet temperature until the bed product temperature reached 40 °C. The resulting enteric coated beads had an average particle diameter of 1 mm.

Table 1 lists the composition of the enteric coated beads prepared in this example. The composition is reported as weight % of each ingredient based on the total weight of the enteric coated bead. It should be again noted that the subcoat layer is optional.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredients</strong></td>
</tr>
<tr>
<td><strong>A. Coated particles</strong></td>
</tr>
<tr>
<td>Sugar spheres</td>
</tr>
<tr>
<td>Ixabepilone</td>
</tr>
<tr>
<td>Binder</td>
</tr>
<tr>
<td>tris (hydroxymethyl) aminomethane</td>
</tr>
<tr>
<td><strong>B. Subcoat Layer</strong></td>
</tr>
<tr>
<td>Subcoat</td>
</tr>
<tr>
<td><strong>C. Enteric Coating</strong></td>
</tr>
<tr>
<td>methacrylic acid copolymer</td>
</tr>
</tbody>
</table>
Table/Capsule Preparation Example 2

Preparation of Active Ingredient Suspension

An active ingredient suspension was prepared containing ixabepilone. First, 2.7832 g Tris powder (tris(hydroxymethyl aminomethane)), 484.5 g water, and 12.7 g 1 N HCl were mixed to provide a 0.046 M Tris buffer solution having a pH of 8.1 ±0.1. Next, a mixture of 33.6 g of Tris buffer solution and 4 g of ixabepilone, as crystals, was added and stirred. To this mixture 2.4 g Opadry™ Clear Coat powder (Colorcon, Inc., PA), as the binder, was added and stirred for approximately 30 minutes to provide the active ingredient suspension. The active ingredient suspension was passed through a 60 mesh screen to remove agglomerates.

Preparation of Drug Coated Particles

The coated particles were prepared by applying the active ingredient suspension onto base particles. The base particles were 14/18 mesh sugar beads, (Sugar Spheres, NF particles, (Chr. Hansen, Inc., WI)) having particle diameters of greater than 1 mm and less than 1.4 mm.

The active ingredient suspension was applied to the base particles by spraying using a fluid bed processor that was set up as a Wuster spray coating system. The spray coating system included an Aeromatic-Fielder MP-MICRO™ fluid bed processor (Niro Inc., Maryland) equipped with a 0.8 mm spray tip. The fluid bed processor was charged with 70 g of the sugar beads and then preheated to 30-50°C. The active ingredient suspension was applied to the base particles with the following application and drying parameters: a spray rate of 1.0 to 1.2 g/minute with a spray atomization pressure of 1.8 bar (180 kilopascals), an inlet temperature of 65-70 °C, an outlet temperature of 28-32°C, a product bed temperature of 27-32°C, and a fan speed of 3.8 to 4.2 m³/hr. During the application process, the active ingredient suspension was slowly stirred.

After application of the active ingredient suspension was completed, the inlet temperature was maintained at the final inlet temperature until the bed product

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl phthalate</td>
<td>5.19</td>
</tr>
<tr>
<td>NaOH</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>
temperature reached 38-42°C. The other alternative is to immediately continue the spray with the subcoat and dry at the end of that process.

**Application of Subcoat Layer**

A subcoat was applied to the drug coated particles. The subcoat solution was prepared by combining 8 g Opadry™ Clear Coat powder and 92 g water and stirring until a clear solution was obtained.

In the subcoating procedure, the fluid bed processor used to prepare the coated particles was employed. Drug coated particles (65 g), were preheated to approximately 30-50°C in the fluid bed processor. The subcoat layer was applied using the application and drying parameters disclosed hereinabove to the preparation of the coated particles. During the application process, the subcoated solution was slowly stirred. After application of the subcoat solution was completed, the inlet temperature was maintained at the final inlet temperature until the bed product temperature reached 38-42 °C.

**Application of Enteric Coating**

An enteric coating was applied onto the drug coated particles having a subcoat. The enteric coating solution was prepared by first filtering Eudragit™ L30D55 polymer dispersion (Röhm GmbH and Co., Darmstadt, Germany) through a 60 mesh screen. Eudragit™ L30D55 polymer dispersion is an aqueous suspension containing methacrylic acid copolymer. The filtered Eudragit polymer dispersion (133.34 g) was diluted with 55.61 g water. Next, 6 g diethyl phthalate was added to the diluted Eudragit polymer dispersion, followed by the addition of 5.05 g of 1 N NaOH solution. The pH of the resulting enteric coating solution was 5.0±0.1.

In the enteric film coating procedure, the fluid bed processor used to prepare the drug coated particles was employed. The fluid bed processor, which contained 65 g of the sub-coated particles, was preheated to 30-50°C. The enteric coating solution was applied using the following application and drying parameters: 0.8 mm spray tip, 1.0 to 1.2 g/minute spray rate, spray atomization pressure was 1.8 bar, inlet temperature 65-70°C, outlet temperature 30-36°C, product bed temperature 28-32°C, and fan speed of 3.9-4.1 m³/hr. During the application process, the enteric coating solution was slowly stirred. After application of the enteric coating solution was completed, the inlet temperature was maintained at the final inlet temperature until the bed product
temperature reached 38-42 °C. The resulting enteric coated beads had an estimated average particle diameter of 1.4 mm.

Table 2 lists the composition of the enteric coated beads prepared in this example. The composition is reported as weight % of each ingredient based on the total weight of the enteric coated bead. It should be again noted that the subcoat layer is optional.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Coated particles</td>
<td></td>
</tr>
<tr>
<td>Sugar spheres</td>
<td>71.0538</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>2.2220</td>
</tr>
<tr>
<td>Opadry Clear</td>
<td>1.3332</td>
</tr>
<tr>
<td>tris (hydroxymethyl) aminomethane (solids)</td>
<td>0.1039</td>
</tr>
<tr>
<td>1N HCl (solids)</td>
<td>0.0171</td>
</tr>
<tr>
<td>B. Subcoat Layer</td>
<td></td>
</tr>
<tr>
<td>Opadry Clear</td>
<td>3.1100</td>
</tr>
<tr>
<td>C. Enteric Coating</td>
<td></td>
</tr>
<tr>
<td>methacrylic acid copolymer (Eudragit L30D55)</td>
<td>19.0017</td>
</tr>
<tr>
<td>Diethyl phthalate</td>
<td>2.8501</td>
</tr>
<tr>
<td>1N NaOH (solids)</td>
<td>0.1082</td>
</tr>
<tr>
<td>D. Talc Addition</td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>0.2000</td>
</tr>
<tr>
<td>Total</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Table/ Capsule Preparation Example 3**

Enteric coated beads comprising ixabepilone were prepared as described below. A summary of the enteric coated bead compositions is shown in Table 3. As can be seen, the subcoat layer and pre-coat layer are optional.
<table>
<thead>
<tr>
<th>3.1</th>
<th>yes-buffered</th>
<th>buffered</th>
<th>yes</th>
<th>yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2</td>
<td>no</td>
<td>buffered</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>3.3</td>
<td>no</td>
<td>buffered</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>3.4</td>
<td>no</td>
<td>nonbuffered</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>3.5</td>
<td>no</td>
<td>nonbuffered</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

All coatings were prepared in Aeromatic-Fielder Type MP Micro fluid bed unit fitted with bottom spray. The coating set-up was as follows: charge (50-90 g), column setting (1 cm), spray nozzle diameter (0.8 mm), atomization pressure (1.8 bar), spray rate (0.9-1.1 b/minute), fan speed 3.5-4.0 m³/hr, inlet temperature (58-72°C), bed temperature (30-33°C). At the end of each coating step, product was dried further until a bed temperature of approximately 40°C was reached.

The size of the sugar beads was 18/20 mesh. The coating solutions and suspensions used were as follows:

Buffered Opadry Pre-coat: This consisted of 8% (w/w) solution of Opadry® Clear (YS-1-19025-A) in 0.046 M Tris buffer (pH 8.1 ± 0.1). Applied to obtain ~4% weight gain.

Opadry Sub coat: This consisted of 8% (w/w) solution of Opadry® Clear in MilliQ water. Applied to obtain ~4% weight gain.

Buffered Drug Coat: This consisted of 5% (w/w) solution of Opadry® Clear in 0.046 M Tris buffer (pH 8.1 ± 0.1) containing 12% (w/w) ixabepilone. Applied to obtain ~3.7% weight gain.

Un-buffered Drug Coat: This consisted of 5% (w/w) solution of Opadry® Clear in MilliQ water and containing 12% (w/w) ixabepilone. Applied to obtain ~3.7% weight gain.

Enteric Coat: This consisted of 66.67% (w/w) Eudragit® L30D-55 (30% solids), 3% diethyl phthalate in MilliQ water and the suspension pH was adjusted to 5.0 ± 0.1 with 1N NaOH. Applied to obtain ~35% weight gain.
The enteric coated beads of Capsule Preparation Examples 3.1-3.5 were placed in scintillation glass vials and stored at 40°C for 8 weeks. The enteric coated beads were assayed by HPLC using the following assay procedure:

5 Column: YMC-Pack Pro C8, 150*4.6 mm, 3mm. S/N
Mobile Phase A: 10mM NH₄OAc in water : acetonitrile (90:10) (NH₄OAc, Sigma)
Mobile Phase B: 10mM NH₄OAc in water : acetonitrile (30:70) (ACN: EM Science)
Flow Rate: 1.5 mL/min
Detection: UV at 240 nm

10 Injection Volume: 10mL
Needle washing sol: Water:acetonitrile (50:50)
Column Temperature: Ambient
Sample Temperature: 4°C
Gradient: % Mobile % Mobile

15 Time (min) Phase A Phase B
0-2 80 20
2-36 80-69.5 20-30.5
36-51 69.5-20 30.5-80
51-56 20-80 80-20
56-71 80 20

Diluent: acetonitrile (EM Science)
Standard Solution: (0.2mg/mL, ixabepilone, Purity 99.3%)

25 The standard solution was prepared by weighting ~50.0 mg ixabepilone into a 250 mL volumetric flask, followed by the addition of 100 mL diluent. The mixture was sonicated for about 5 minutes or until the solid material was dissolved. The solution was stored at 4°C for up to 7 days.

The enteric coated beads were prepared for assay using a Tablet Process

30 Workstation (Caliper Lifescience, Hopkinton, MA). Sample preparation: (0.2mg/mL).
CLAIMS

We claim:

1. Use of ixabepilone, in the manufacture of a medicament for treating cancer in a human patient, wherein said medicament is orally administered to said human patient according to a dosing schedule wherein the dose of said medicament comprises a cycle dose that is split into two or more oral unit dosages administered on Day 1 of an intermittent dosing cycle.

2. Use of ixabepilone according to claim 1, wherein the dosing schedule comprises 3 oral unit dosages separated by 6 hours on Day 1, wherein the oral unit dosage is independently at each administration selected from 10 to 60 mg of ixabepilone (more preferably from 20-55 mg ixabepilone, and more preferably from 45 to 55 mg ixabepilone).

3. Use of ixabepilone according to claims 1 or 2, wherein the intermittent dosing cycle is selected from 10, 15, and 21-day cycles, and administration of the split oral unit dosage is repeated at intervals of 10, 15 and 21 days, respectively.

4. Use of ixabepilone as in claims 1, 2, or 3, wherein the unit dosage at each administration is independently selected from 20 mg, 30 mg, 40 mg and 50 mg ixabepilone.

5. Use of ixabepilone as in any one of claims 1, 2, 3, or 4, wherein the cycle dose is 100 to 160 mg (more preferably 145 to 155 mg, and even more preferably 150 mg).

6. Use of ixabepilone as in any one of claims 1, 2, 3, 4, or 5, wherein a unit dosage of 45 to 55 mg (more preferably, 50 mg) is administered three times on Day 1 of the dosing cycle and each unit dosage is separated by a period of 4 to 8 hours (more preferably, by 5 hours).
7. Use of ixabepilone as in any one of claims 1, 2, 3, 4, 5, or 6, wherein the dosing cycle is every 21 days.

8. Use of ixabepilone according to any one of claims 1 to 7, wherein the medicament further comprises a combination with a unit dosage of one or more inhibitors of CYP3A4/5 enzymes (preferably ketoconazole), for concurrent or sequential use.

9. Use of ixabepilone, according to any one of claims 1 through 7, wherein the cancer is selected from breast, prostate, small cell lung, and/or renal cancer.
FIG. 1

In mice bearing sc M109 lung carcinoma efficacy can be dissociated from neurotoxicity
FIG. 2

In mice bearing sc M5076 Taxol resistant fibrosarcoma
Split Dose Improved Efficacy

- Control
- Ixabepilone (10 mpk, once-a-day, Q4Dx3)
- Ixabepilone (5 mpk, BID, Q4Dx3)
- Taxol (36 mpk, Q2Dx5)

Median tumor wt. (mg)

Days post-tumor implant
FIG. 3

In mice bearing sc 16/C mammary carcinoma
Split Dose Improved Efficacy

- Control
- Ixa (PO, BID, Q4Dx3, 24 mpk)
- Ixa (PO, once-a-day, Q4Dx3, 48 mpk)

Days post-tumor implant vs Median tumor wt (mg)
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K31/427 A61P35/00

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Relevant to claim No.</th>
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**X** Further documents are listed in the continuation of Box C.  
See patent family annex.

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- **E** earlier document but published on or after the international filing date
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**Date of the actual completion of the international search**

6 May 2009

**Date of mailing of the international search report**

13/05/2009

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax. (+31-70) 340-3016

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Albayrak, Timur

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