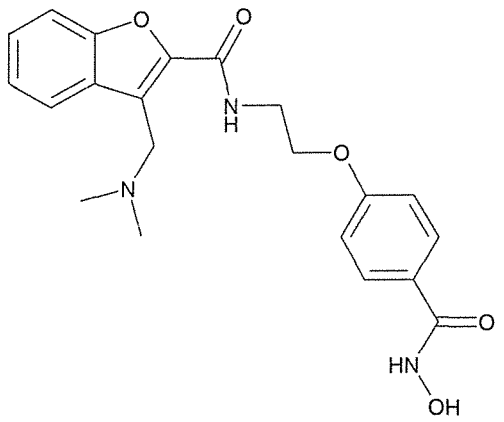
NEW ADMINISTRATION REGIME FOR *N*-HYDROXY-4-{2-[3-(*N*,*N*-DIMETHYLAMINOMETHYL)BENZOFURAN-2-YLCARBONYLAMINO]ETHOXY}BENZAMIDE

The present invention relates to a new administration regime for *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide of formula (I):



(I),

or an addition salt thereof with a pharmaceutically acceptable acid or base, alone or in association with a surgery, chemotherapy, hormone therapy treatment or radiotherapy, for the treatment of cancer.

N-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide is a powerful histone deacetylase (HDAC) inhibitor described in patent application WO2004/092115. It allows inhibition of cell growth and induces apoptosis in cultured tumour cells *in vitro*, and it inhibits tumour growth *in vivo* in xenograft models (Buggy *et al., Mol. Cancer Ther* **2006** 5(5) 1309). Its pharmacological profile makes it of major therapeutic value in the treatment of cancer.

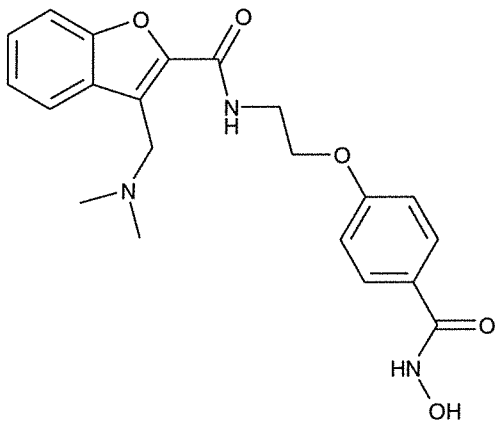
In the present invention it has been established that *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide of formula (I) has a very advantageous therapeutic index in the treatment of cancer when it is administered for 4 consecutive days, that period being followed by 3 consecutive days without any administration of compound of formula (I).

More specifically, it has been shown that the maximum tolerated dose of *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide was considerably increased in patients suffering from cancer when it was administered for 4 consecutive days, that period being followed by 3 consecutive days without any

administration of compound of formula (I). That administration cycle is repeated as many times as necessary for the cancer treatment. Alternatively, those weekly administration cycles may be periodically broken up by a week without any treatment.

This administration regime makes it possible to envisage better use of the *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide in that it makes it possible to minimise the platelet toxicity inherent to the product whilst allowing sufficient exposure for the cancer treatment.

The present invention relates to *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl) benzofuran-2-ylcarbonylamino]ethoxy}benzamide of formula (I):



(I),

or an addition salt thereof with a pharmaceutically acceptable acid or base, alone or in association with a surgery, chemotherapy, hormone therapy treatment or radiotherapy, for use in the treatment of cancer, characterised in that it is administered for 4 consecutive days, that period being followed by 3 consecutive days without any administration of compound of formula (I), with the proviso that chemotherapy is not FOLFOX (oxaliplatin/folinic acid/ 5-fluorouracil).

In the context of the invention, preference is given to using the *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide in the form of a hydrochloride.

The *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]-ethoxy}benzamide is advantageously administered for 4 consecutive days at the rate of 2 administrations per day, that period being followed by 3 consecutive days without any administration of compound of formula (I).

In certain embodiments, the cancer treated according to the administration regime of the invention may be a carcinoma, a tumour, a neoplasm, a lymphoma, a melanoma, a glioma, a sarcoma or a blastoma. The administration regime according to the invention is especially useful in the treatment of solid tumours, and even more especially in the treatment of breast cancer. Epithelial ovarian, fallopian tube and primary peritoneal carcinoma are also specifically targeted.

Preferably, the *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-yl-carbonylamino]ethoxy}benzamide is administered according to the administration regime of the invention in association with a chemotherapy or hormone therapy treatment or radiotherapy.

In certain embodiments, the *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide is administered for 4 consecutive days, that period being followed by 3 consecutive days without any further administration of that compound, in association with a chemotherapy treatment selected from doxorubicin, pegylated liposomal doxorubicin, cisplatin, cyclophosphamide, paclitaxel, carboplatin, carboplatin/paclitaxel, cisplatin/doxorubicin/cyclophosphamide, pegylated liposomal doxorubicin/cisplatin. More preferably, the associated chemotherapy treatment is doxorubicin, pegylated liposomal doxorubicin or cisplatin.
Alternatively, the *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-yl-carbonylamino]ethoxy}benzamide is administered for 4 consecutive days, that period being followed by 3 consecutive days without any further administration of that compound, in association with tamoxifen as hormone therapy treatment.

In a preferred embodiment, the *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)-benzofuran-2-ylcarbonylamino]ethoxy}benzamide is administered orally.

The useful dosage varies according to the sex, age and weight of the patient, the administration route, the nature of the cancer and any associated treatments and ranges from 30 mg/m^2 to 210 mg/m^2 of *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzo-furan-2-ylcarbonylamino]ethoxy}benzamide hydrochloride per day. More generally, the useful dosage ranges from 20 mg to 480 mg of *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzo-furan-2-ylcarbonylamino]ethoxy}benzamide expressed as a base per day.

Clinical study 1: *(N-hydroxy-4-{2-[3-(N,N-dimethylaminomethyl)benzofuran-2-yl-carbonylamino]ethoxy}benzamide in monotherapy)*

A clinical study was set up to test the toxicity and efficacy of *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride. 36 patients with solid tumours were included and treated in this study. A first administration regime was tested over a cycle of three weeks, with 14 consecutive days of 2 *p.o.* administrations 4 hours apart, followed by a week without treatment. Four dosage levels were successively tested from 30 to 75 mg/m^2 (expressed as a salt) twice daily.

The acceptability of the various *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)-benzofuran-2-ylcarbonylamino]ethoxy}benzamide dose levels were evaluated (especially, haematological toxicities) at the end of the first cycle.

The results showed that all the toxicities which limited increasing the dose were grade 4 thrombopenias (blood platelet level less than 25 giga per litre), which were reversible after ceasing the *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonyl-amino]ethoxy}benzamide treatment (see Figure 1). The maximum tolerated dose according to this first administration regime was established to be 75 mg/m^2 twice daily.

In order to avoid the substantial reductions in the number of platelets observed using that regime, the study protocol was amended to propose a new administration regime: 4 consecutive days of 2 *p.o.* administrations 4 hours apart and then 3 days without treatment, that regime being applied for each of the 3 weeks corresponding to an administration cycle. This cycle can be repeated as many times as necessary for treatment of the cancer. This new regime showed less platelet toxicity than the previous regime and allowed patients to

be treated at higher dose levels (90 to 105 mg/m^2 twice daily). By way of comparison, Figure 2 shows that the second administration regime is substantially less detrimental than the first as regards blood platelet level at a dose of 75 mg/m^2 twice daily. In the second administration regime, the recommended dose and the maximum tolerated dose were established to be 90 mg/m^2 and 105 mg/m^2 twice daily, respectively.

Clinical study 2: *(N-hydroxy-4-{2-[3-(N,N-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide in combination with cisplatin)*

A phase I clinical study for testing the association of *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride with cisplatin is carried out on about forty patients with various solid tumours. The patients receive a maximum of six cycles of treatment with the association, each of the cycles taking the following form: the *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride is administered for 4 consecutive days followed by 3 consecutive days without treatment, that being carried out for the first two weeks of a cycle of three weeks. The cisplatin is administered on the third day of each treatment cycle. No treatment is administered during the third week of the cycle.

On the relevant days, the daily dose of *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride is between 80 and 320 mg inclusive (expressed as a base), comprising two *p.o.* administrations 4 hours apart. The cisplatin is administered at a fixed dose of 75 mg/m^2.

At the end of a treatment cycle, the toxicity of the protocol involving *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride and cisplatin in association is evaluated. If no prohibitive toxicity is observed, the patient continues the treatment. Every two cycles, the efficacy of the treatment is assessed via evaluation of the tumour response (CT scan, MRI, ...). The acceptability profile is also evaluated (especially, haematological and cardiac toxicities). The patient continues the combination treatment for a maximum of six cycles.

Clinical study 3: *(N-hydroxy-4-{2-[3-(N,N-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide in combination with doxorubicin)*

A phase I clinical study for testing the association of *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride with doxorubicin in the treatment of advanced solid tumours is carried out on about forty patients. The patients receive a maximum of six cycles of treatment with the association, each of the cycles taking the following form: the *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride is administered for 4 consecutive days followed by 3 consecutive days without treatment, that being carried out for the first three weeks of a cycle of four weeks. The doxorubicin is infused on the third day of the first three weeks of the cycle. No treatment is administered during the fourth week of the cycle.

On the relevant days, the daily dose of *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride is between 60 and 150 mg/m^2 inclusive (expressed as a salt), comprising two *p.o.* administrations 4 hours apart. The doxorubicin is administered at a fixed dose of 25 mg/m^2.

At the end of a treatment cycle, the toxicity of the protocol involving *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride and doxorubicin in association is evaluated. If no prohibitive toxicity is observed, the patient continues the treatment. Every two cycles, the efficacy of the treatment is assessed via evaluation of the tumour response (CT scan, MRI, ...). The acceptability profile is also evaluated (especially, haematological and cardiac toxicities). The patient continues the combination treatment for a maximum of six cycles.

Clinical study 4: *(N-hydroxy-4-{2-[3-(N,N-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide in combination with pegylated liposomal doxorubicin)*

A phase I clinical study for testing the association of *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride with pegylated liposomal doxorubicin in the treatment of primary platinum-resistant and partially platinum-sensitive, epithelial ovarian, fallopian tube or primary peritoneal

carcinoma is carried out on about seventy patients. The patients are subjected to cycles of treatment of four weeks with the association. Two schedules are tested:

- Schedule 1: the *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride is administered for 4 consecutive days followed by 3 consecutive days without treatment, that being carried out for the first three weeks of a cycle of four weeks. The pegylated liposomal doxorubicin is infused on the third day of the first week of the cycle. No treatment is administered during the fourth week of the cycle.
- Schedule 2: the *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride is administered for 4 consecutive days followed by 3 consecutive days without treatment in the first week of a cycle of four weeks. The pegylated liposomal doxorubicin is infused on the third day of the first week of the cycle. No treatment is administered during the three last weeks of the cycle.

On the relevant days, the daily dose of *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride is between 60 and 150 mg/m^2 inclusive (expressed as a salt), comprising two *p.o.* administrations 4 hours apart. The pegylated liposomal doxorubicin is administered at a fixed dose of 40 mg/m^2.

At the end of a treatment cycle, the toxicity of the protocol involving *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride and pegylated liposomal doxorubicin in association is evaluated. If no prohibitive toxicity is observed, the patient continues the treatment. Every two cycles, the efficacy of the treatment is assessed via evaluation of the tumour response (CT scan, MRI, ...). The acceptability profile is also evaluated (especially, haematological and cardiac toxicities).

Clinical study 5: *(N-hydroxy-4-{2-[3-(N,N-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide in combination with tamoxifen)*

A phase I clinical study for testing the association of *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride

with tamoxifen in the treatment of advanced breast cancer is carried out on about forty patients. The patients are subjected to cycles of treatment with the association, each of the cycles taking the following form: the *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride is administered for 4 consecutive days followed by 3 consecutive days without treatment. The tamoxifen is administered daily throughout the duration of the treatment.

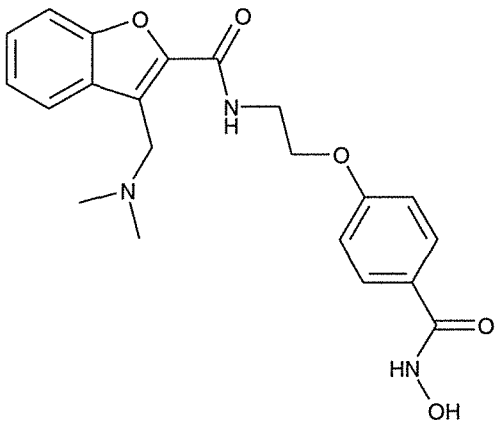
On the relevant days, the daily dose of *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride is between 160 and 320 mg inclusive (expressed as a base), comprising two *p.o.* administrations 4 hours apart. The tamoxifen is administered at a fixed dose of 20 mg.

At the end of two treatment cycles, the toxicity of the protocol involving *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide hydrochloride and tamoxifen in association is evaluated. If no prohibitive toxicity is observed, the patient continues the treatment. Every two cycles, the efficacy of the treatment is assessed via evaluation of the tumour response (CT scan, MRI, ...). The acceptability profile is also evaluated (especially, haematological and cardiac toxicities).

The various clinical studies hereinbefore show that an administration regime in which *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide is administered for 4 consecutive days, that period being followed by 3 consecutive days without any administration, makes it possible to minimise the platelet toxicity inherent to the product and thereby to increase the therapeutic dose for the treatment of cancer.

CLAIMS

1- *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]-ethoxy}benzamide of formula (I):



(I),

or an addition salt thereof with a pharmaceutically acceptable acid or base, alone or in association with a surgery, chemotherapy, hormone therapy treatment or radiotherapy, for use in the treatment of cancer, characterised in that it is administered for 4 consecutive days, that period being followed by 3 consecutive days without any administration of compound of formula (I), with the proviso that chemotherapy is not FOLFOX (oxaliplatin/folinic acid/ 5-fluorouracil).

2- Compound of formula (I) according to claim 1, characterised in that it is used in the form of a hydrochloride.

3- Compound of formula (I) according to either claim 1 or claim 2, characterised in that it is administered for 4 consecutive days at a rate of 2 administrations per day, that period being followed by 3 consecutive days without any administration of compound of formula (I).

4- Compound of formula (I) according to one of claims 1 to 3 administered in association with a chemotherapy or hormone therapy treatment or radiotherapy.

5- Compound of formula (I) according to one of claims 1 to 4 for use in the treatment of carcinoma, tumours, neoplasm, lymphoma, melanoma, glioma, sarcoma or blastoma.

6- Compound of formula (I) according to one of claims 1 to 5 for use in the treatment of solid tumours.

7- Compound of formula (I) according to one of claims 1 to 5 for use in the treatment of breast cancer.

8- Compound of formula (I) according to one of claims 1 to 5 for use in the treatment of epithelial ovarian, fallopian tube or primary peritoneal carcinoma.

9- Compound of formula (I) according to one of claims 1 to 5, characterised in that the chemotherapy treatment is cisplatin, doxorubicin or pegylated liposomal doxorubicin.

10- Compound of formula (I) according to one of claims 1 to 5, characterised in that the hormone therapy treatment is tamoxifen.

11- Use of a compound of formula (I) according to one of claims 1 to 3, or an addition salt thereof with a pharmaceutically acceptable acid or base, alone or in association with a surgery, chemotherapy, hormone therapy treatment or radiotherapy, in the treatment of carcinoma, tumours, neoplasm, lymphoma, melanoma, glioma, sarcoma or blastoma.

12- Use of a compound of formula (I) according to claim 11 in association with a chemotherapy or hormone therapy treatment or radiotherapy.

13- Use of a compound of formula (I) according to claim 11 in the treatment of solid tumours.

14- Use of a compound of formula (I) according to claim 11 in the treatment of breast cancer.

15- Use of a compound of formula (I) according to claim 11 in the treatment of epithelial ovarian, fallopian tube or primary peritoneal carcinoma.

16- Use of a compound of formula (I) according to claim 11 wherein the chemotherapy treatment is cisplatin, doxorubicin or pegylated liposomal doxorubicin.

17- Use of a compound of formula (I) according to claim 11 wherein the hormone therapy treatment is tamoxifen.