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- (54) **NEUROENDOCRINE TUMOR TREATMENT**
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(57) **ABSTRACT**
 A method for treating endocrine tumors by administration of an mTOR inhibitor, optionally in combination with another drug.



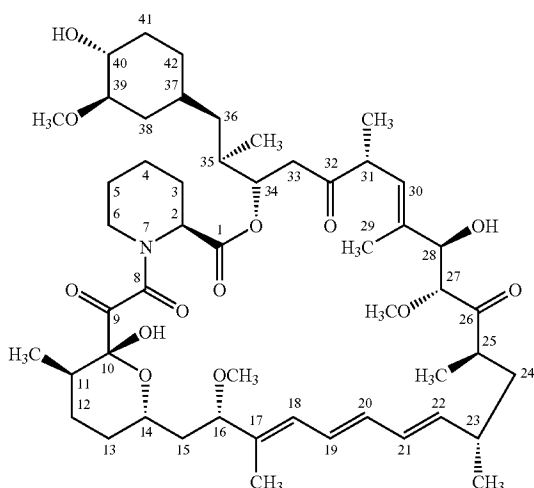
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NEUROENDOCRINE TUMOR TREATMENT

The present invention relates to organic compounds, more specifically to the use of mTOR inhibitors in neuroendocrine tumor treatment.

An mTOR inhibitor as used herein is a compound which targets intracellular mTOR ("mammalian Target of rapamycin"). mTOR is a family member of phosphatidylinositol 3-kinase (PI3-kinase) related kinase. The compound rapamycin and other mTOR inhibitors inhibit mTOR activity via a complex with its intracellular receptor FKBP12 (FK506-binding protein 12). mTOR modulates translation of specific mRNAs via the regulation of the phosphorylation state of several different translation proteins, mainly 4E-PB1, P70S6K (p70S6 kinase 1) and eEF2.

Rapamycin is a known macrolide antibiotic produced by *Streptomyces hygroscopicus* of formula



Other mTOR inhibitors include rapamycin derivatives, for example including rapamycin substituted in position 40 and/or 16 and/or 32.

Examples of other mTOR inhibitors include 40-O-alkyl-rapamycin derivatives, e.g. 40-O-hydroxyalkyl-rapamycin derivatives, for example 40-O-(2-hydroxy)ethyl-rapamycin (everolimus),

rapamycin derivatives which are substituted in 40 position by heterocyclyl, e.g. 40-epi-(tetrazolyl)-rapamycin (also known as ABT578),

32-deoxo-rapamycin derivatives and 32-hydroxy-rapamycin derivatives, such as 32-deoxorapamycin,

16-O-substituted rapamycin derivatives such as 16-pent-2-ynyloxy-32-deoxorapamycin, 16-pent-2-ynyloxy-32(S or R)-dihydro-rapamycin, or 16-pent-2-ynyloxy-32(S or R)-dihydro-40-O-(2-hydroxyethyl)-rapamycin,

rapamycin derivatives which are acylated at the oxygen in position 40, e.g. 40-[3-hydroxy-2-(hydroxy-methyl)-2-methylpropanoate]-rapamycin (also known as CCI779 or temsirolimus),

rapamycin derivatives (also sometimes designated as rapalogs) as disclosed in WO9802441 or WO0114387, e.g. including AP23573, such as 40-O-dimethylphosphinyl-rapamycin, compounds disclosed under the name biolimus (biolimus A9), including 40-O-(2-ethoxy)ethyl-rapamycin, and com-

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mTOR inhibitors as e.g. disclosed in WO2004101583, WO9205179, WO9402136, WO9402385 and WO9613273.

Preferred mTOR inhibitors include

rapamycin, and/or

40-O-(2-hydroxyethyl)-rapamycin, and/or

32-deoxorapamycin, and/or

16-pent-2-ynyloxy-32-deoxorapamycin, and/or

16-pent-2-ynyloxy-32 (S or R)-dihydro-rapamycin, and/or

16-pent-2-ynyloxy-32 (S or R)-dihydro-40-O-(2-hydroxyethyl)-rapamycin, and/or

40-[3-hydroxy-2-(hydroxy-methyl)-2-methylpropanoate]-

rapamycin (also known as CCI779) and/or

40-epi-(tetrazolyl)-rapamycin (also known as ABT578), and/or

the so-called rapalogs, e.g. as disclosed in WO9802441,

WO0114387 and WO0364383, AP23573, AP23464,

AP23675 or AP23841, e.g. AP23573, and/or

compounds disclosed under the name TAFE-93, and/or

compounds disclosed under the name biolimus.

More preferably an mTOR inhibitor is selected from the group consisting of rapamycin, and/or

40-O-(2-hydroxyethyl)-rapamycin, and/or

32-deoxorapamycin, and/or

16-pent-2-ynyloxy-32-deoxorapamycin, and/or

16-pent-2-ynyloxy-32 (S or R)-dihydro-rapamycin, and/or

16-pent-2-ynyloxy-32 (S or R)-dihydro-40-O-(2-hydroxyethyl)-rapamycin, and/or

40-[3-hydroxy-2-(hydroxy-methyl)-2-methylpropanoate]-

rapamycin (also known as CCI779) and/or

40-epi-(tetrazolyl)-rapamycin (also known as ABT578), and/or

AP23573,

such as 40-O-(2-hydroxyethyl)-rapamycin.

mTOR inhibitors, on the basis of observed activity, have been found to be useful e.g. as immunosuppressant, e.g. in the

treatment of acute allograft rejection and have additionally potent antiproliferative properties which make them useful

for cancer chemotherapy, particularly for the treatment of solid tumors, especially of advanced solid tumors.

Endocrine, e.g. neuroendocrine tumors (NETs), are found in the endocrine system. Carcinoid tumors, are a special type

of tumor, generally classified as endocrine tumors. Carcinoid tumors belong to the family of neuroendocrine tumors which

derive from the neuroendocrine cell system. In the intestinal tract, these tumors develop deep in the mucosa, growing

slowly and extending into the underlying submucosa and mucosal surface. This results in the formation of small firm

nodules, which bulge into the intestinal lumen. Pancreatic neuroendocrine tumors (islet cell tumors), which were

formerly classified as APUDomas (tumors of the amine precursor uptake and decarboxylation system), comprise less than

half of all neuroendocrine tumors and only 1-2% of all pancreatic tumors. Pancreatic NETs can arise either in the pan-

creas (insulinomas, glucagonomas, nonfunctioning pancreatic NETs, pancreatic NETs causing hypercalcemia) or at

both pancreatic and extrapancreatic sites (gastrinomas, VIPomas, somatostatinomas, GRFomas). The hormones secreted

by pancreatic NETs depend upon the cell of origin and are physiologically involved in a network of autocrine, paracrine,

endocrine and neurotransmitter communication. While hormone secretion is not observed in all cases of pancreatic NET,

the apparently "nonfunctioning" (i.e., non-secreting) pancreatic NETs tend to be more aggressive and present with symp-

toms of tumor bulk (see e.g. Barakat et al, Endocrine-related

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All pancreatic NETs, with the exception of 90% of insulinomas, have long-term metastatic potential. Most are overtly malignant at the time of diagnosis, and 60% or more present with liver metastases. The most common cause of death from pancreatic NET is hepatic failure (Warner R R P, *Gastroenterology* 2005; 128:1668-16842005).

In a recent review, the 5-year survival rate in a series of 83 consecutive patients with pancreatic NETs has been reported to be 55.3% which points to an unmet medical need for continued treatment in patients with pancreatic NETs whose disease has progressed following 1 or more courses of chemotherapy.

Carcinoid tumors have historically been classified, according to their point of origin in embryonic development, as arising from the foregut (e.g., bronchial, pulmonary or gastric carcinoid), midgut (e.g., small intestine or appendiceal carcinoid), or hindgut (e.g., rectal carcinoid), see e.g. Kulke M., *Cancer Treatment Reviews* 2003; 29:363-370.

Primary foregut tumors are confined to the thymus, lung, stomach, and duodenum. Midgut carcinoids are located in the distal ileum, cecum, and proximal colon. One interesting subset of this group is appendiceal carcinoids, which are often benign and rarely give rise to metastatic disease. The midgut carcinoids dominate the malignant carcinoid tumors, particularly when the carcinoid syndrome is present.

The hindgut tumors are primarily located in the distal colon and rectum.

Data suggest that the incidence of pulmonary and gastric carcinoid has increased in the past two decades.

According to histopathologic criteria, carcinoids can be divided into typical (TC) and atypical (AC) carcinoids. Carcinoids can be placed in a spectrum of neuroendocrine tumors, ranging from low-grade malignant TC to intermediate AC to high-grade large-cell neuroendocrine carcinoma and small-cell lung carcinoma.

Carcinoid lung tumors e.g. include neuroendocrine carcinoma, Kulchitsky cell carcinoma (KCC), bronchial carcinoid tumors, bronchial adenomas, typical carcinoids, atypical carcinoids, carcinoid syndrome, small-cell carcinomas, Kulchitsky cells, argentaffin cells, pulmonary carcinoids, neuroendocrine lung tumors, (primary) pulmonary neoplasms, bronchopulmonary carcinoid tumors, lung neoplasms, lung cancers, pulmonary cancers, intrabronchial mass.

Bronchial carcinoid tumors may originate from the neurosecretory cells of bronchial mucosa and were previously classified as bronchial adenomas. Bronchial carcinoids are now classed as low-grade malignant neoplasms because of their potential to cause local invasion, their tendency for local recurrence, and their occasional metastases to extrathoracic sites.

Bronchial carcinoids belong to a group of neuroendocrine tumors, which cover a range of tumors ranging from bronchial carcinoid at one of the spectrum, with a small cell carcinoma, or possibly large cell neuroendocrine tumors at the other end. They demonstrate a wide range of clinical and biologic behaviors, including the potential to synthesize and secrete peptide hormones and neuroamines, particularly adrenocorticotrophic hormone (ACTH), serotonin, somatostatin, and bradykinin.

Bronchial carcinoid tumors may arise from Kulchitsky cells (argentaffin cells) within the bronchial mucosa. The predominant distribution of cells are believed to occur at the bifurcation of the lobar bronchi. These cells are neurosecretory cells, which belong to the amine precursor uptake and

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releasing mechanism. They produce a variety of hormones, including ACTH, norepinephrine, bombesin, calcitonin, antidiuretic hormone (ADH), and bradykinin.

Large-cell neuroendocrine carcinoma of the lung is a newly recognized clinicopathologic entity, which is distinct from small-cell carcinoma and has a poor prognosis.

Typical carcinoid tumors of the lung represent the most well differentiated and least biologically aggressive type of pulmonary neuroendocrine tumor. These tumors characteristically grow slowly and tend to metastasize infrequently. Atypical carcinoid tumors have a more aggressive histologic and clinical picture. They metastasize at a considerably higher rate than do typical carcinoid tumors. Carcinoid syndrome has been reported in association with very large bronchopulmonary carcinoid tumors or in the presence of metastatic disease. It is noted much less frequently in association with carcinoids of pulmonary origin than those originating within the gastrointestinal tract. Endocrine syndromes found in association with small cell carcinoma of the lung are found less commonly with carcinoid tumors of the lung; however, some endocrine abnormalities have been attributed to both typical and atypical pulmonary carcinoid tumors.

Carcinoid tumors of the GI tract may display an aggressive biology similar to that of adenocarcinomas, particularly when they are located in the colon, stomach, and small intestine, see e.g. Modlin I M et al, *Gastroenterology* 2005; 128:1717-1751. For small-intestinal carcinoids, which are the most frequent cause of carcinoid syndrome due to metastatic disease in the liver, the incidence of metastasis increases proportionally with the size of the primary tumor (Tomassetti et al 2001, *ibidem*).

The incidence and survival data available suggest that clinical trials of new anticancer agents in patients with midgut carcinoid tumors may provide the opportunity to address an unmet medical need in a growing segment of the population of patients with carcinoids.

Carcinoid syndrome is caused by hypersecretion of numerous hormone products by the tumor cells, including kinins, prostaglandins, substance P, gastrin, corticotrophin and chromogranin A (see e.g. Davis et al, *Gynecology & Obstetrics* 1973; 137:637-644). Various endocrine or neuroendocrine syndromes can be initial clinical manifestations of either typical or atypical pulmonary carcinoid tumors. Carcinoid syndrome, hypercortisolism and Cushing syndrome, inappropriate secretion of ADH, increased pigmentation secondary to excess MSH, and ectopic insulin production resulting in hypoglycemia are some of the endocrinopathies that can be produced by a pulmonary carcinoid tumor in a patient who is otherwise asymptomatic.

The most common symptoms are hemoptysis, cough, recurrent pulmonary infection, fever, chest discomfort and chest pain, unilateral wheezing, and shortness of breath, flushing and diarrhea. Paraneoplastic syndromes are rare and include carcinoid syndrome, Cushing's syndrome, and ectopic growth hormone-releasing hormone secretion.

Other less frequent symptoms include cardiac manifestations secondary to fibrosis of the endocardium (Jacobsen MB et al, *Eur Heart J* 1995; 16:263-268) which may result in valvular regurgitation (valvular heart disease), with varying degrees of heart failure in patients with cardiac manifestations. Wheezing or asthma-like symptoms, pellagra-like skin lesions with hyperkeratosis, abdominal pain, telangiectasias and paroxysmal hypotension are also seen in a number of patients. Patients with pulmonary carcinoid often show symptoms like recurrent pneumonia, cough, hemoptysis or chest pain. The majority of pulmonary carcinoid tumors are in

syndrome. Early in the course, symptoms are usually episodic and may be provoked by stress, catecholamines, and ingestion of food or alcohol. During acute paroxysms, systolic blood pressure typically falls 20 to 30 mmHg. Endocardial fibrosis can cause valvular heart disease, usually affecting the proximal side of the tricuspid and pulmonary valves and leading to tricuspid insufficiency and secondary right-sided heart failure.

A recent review of chemotherapeutic treatment of carcinoids reports that the sensitivity of these tumors to various cytotoxic drugs is low, and combination does not increase their effectiveness. Based on their review of various combination therapies, including dacarbazine/fluorouracil or 5-fluorouracil/epirubicin, the authors conclude that they are unable to recommend a specific chemotherapeutic regimen for patients with well-differentiated neuroendocrine malignancies of the GI tract (Arnold R, Rinke A et al, *Clinical Gastroenterology* 2005; 19(4):649-656). The apparent refractoriness of such tumors to currently available therapies points to an unmet medical need for treatment in this patient population.

As part of the endocrine system that regulates hormones, the pituitary gland controls many of the other glands through secretion. Our “master gland,” the pituitary makes some hormones, but also acts as an intermediary between the brain and other endocrine glands. Our hormones and the pituitary gland accomplish many homeostatic and specialized functions, like bone growth and uterine contractions.

Neurons carry messages regarding the production of hormones between the pituitary gland and the hypothalamus. Both are located at the base of the brain, nestled in a rounded part of bone, carefully protected. They are connected by a bunch of neurons called the infundibulum. Together, they work to regulate all the hormones that circulate in the bloodstream, controlling things like growth and hair pigmentation. Hormones are the long-distance messengers that can inform cells when to become active or stay dormant. The pituitary gland controls the thyroid, adrenal glands, ovaries and testes, even though it’s only the size of a pea.

There are different parts of the pituitary gland that have selective functions. The posterior lobe, called the neurohypophysis, releases the hormones vasopressin and oxytocin, but doesn’t produce them. Vasopressin is an anti-diuretic that controls how the kidneys absorb water. Oxytocin is a special hormone only present during childbirth to speed contractions. The anterior lobe of the pituitary gland is called the adenohypophysis. It produces a variety of hormones, such as prolactin that stimulates lactation in women. Melanocyte spurs the body to produce melanin for skin and hair pigmentation. Follicle-stimulating hormone indicates where and when hair should grow during development. The very important growth hormone controls bone growth to determine height, especially active during adolescence. Hormones control glands as well. The thyroid reacts to thyrotropin, the adrenal glands are stimulated by adrenocorticotropin, and the sex glands are affected by luteinizing hormone. The pituitary gland is responsible for many stages and aspects of our maturation.

Pituitary tumors are in general noncancerous (benign), comprising only 10 percent of brain tumors. However, because of the location of the pituitary gland, at the base of the skull, a pituitary tumor grows upward. And, eventually, many pituitary tumors press against the optic nerves, causing vision problems. Symptoms vary depending upon what type of tumor is growing and what area of the pituitary gland is affected. Pituitary tumors can cause symptoms that are

Other symptoms may be due to the proximity of these tumors to local brain structures, such as the optic nerves leading to loss of vision. Each individual also experiences symptoms differently, and the symptoms many resemble other conditions or medical problems

The most common type of pituitary tumor is called a clinically nonfunctioning tumor, because patients do not have the classic pituitary syndromes from excess hormones, such as in acromegaly. These types of tumors may be detected during an evaluation of an incidental problem. A clinically nonfunctioning tumor may cause hypopituitarism, or an underactive pituitary gland, which may lead to failure of sexual function, reduced sperm production, and cessation of a woman’s menstrual period, along with fatigue.

Another common pituitary tumor is called a prolactinoma, a benign tumor that produces the prolactin hormone. Prolactin stimulates breast milk production after childbirth. Women with a prolactinoma may have reduced or absent menstrual cycles along with breast milk production.

An uncommon pituitary tumor causes excess growth hormone production (a hormone necessary for normal childhood growth) resulting in acromegaly. In adults, such tumors lead to excessive somatic growth and multiple systemic, medical consequences. Another uncommon pituitary tumor results in Cushing’s disease, a disorder of excess steroid production.

Multiple endocrine neoplasia type 1 (MEN 1) is a relatively uncommon inherited disease. Individuals who inherit the gene for MEN 1 have an increased chance of developing overactivity and enlargement of certain endocrine glands. The endocrine glands most commonly affected by MEN 1 are the parathyroid, pancreas, and pituitary glands. Almost everyone who inherits MEN 1 develops overactivity of the parathyroid glands (hyperparathyroidism) at some stage in their life. The other endocrine glands become overactive less frequently, however, people who inherit MEN 1 will usually develop overactivity in more than one endocrine gland. Overactivity in different endocrine glands may occur simultaneously or at separate times during a persons life. MEN 1 can lead to overactivity and enlargement of the three endocrine glands listed above (the endocrine glands which start with the letter “P”). People who inherit the gene for MEN 1 are predisposed to developing an overactivity in hormone production from the parathyroid glands, pituitary gland and pancreas (that is why physicians will measure hormones in the blood to check for overproduction of each specific hormone). Increased hormone production is usually associated with enlargement of these glands. Endocrine gland enlargement and hormone overproduction does not usually occur in all areas of an endocrine gland at the same point in time. Some parts of overactive endocrine glands grow more rapidly than others, and produce more hormone than other parts of the same gland. The parts of an endocrine gland which grow most rapidly become “lumpy”. These lumps are usually benign. Benign lumps in endocrine glands are known as adenomas.

Adenomas are benign (not cancerous), and do not spread to other parts of the body. Pituitary adenomas (pituitary tumors, nervous system tumor) can lead to nerve damage, growth disturbances, and changes in hormonal balance. Symptoms of pituitary adenomas can vary considerably, largely depending on whether or not the tumor is secreting one or more of a variety of hormones. Even if the tumor is not producing any hormones, its location at the base of the brain can cause significant symptoms. Symptoms may e.g. include double or blurred vision, loss of peripheral vision, sudden blindness, headache, dizziness, loss of consciousness, nausea, weak-

growth of skull, hands, and feet, deepening of voice, changes in facial appearance (due to changes in facial bones), wider spacing of teeth, joint pain, increased sweating, purple stretch marks on the abdomen, increased hair growth, fat deposits where the neck meets the spine, moodiness or depression, easy bruising, palpitations (rapid or irregular heartbeat), tremor, increased appetite, feeling warm or hot, difficulty falling asleep, anxiousness, frequent bowel movements, lump in the front of the neck (enlarged thyroid).

It was found that mTOR inhibitors may be used for the treatment of such special type of tumors

In accordance with the particular findings the present invention provides in several aspects:

- 1.1 A method for treating endocrine tumors, comprising administering to a subject in need thereof a therapeutically effective amount of an mTOR inhibitor.
- 1.2 A method for inhibiting growth of endocrine tumors, comprising administering to a subject in need thereof a therapeutical effective amount of an mTOR inhibitor.
- 1.3 A method for inhibiting or controlling endocrine tumors, comprising administering to a subject in need thereof a therapeutically effective amount of an mTOR inhibitor.
- 1.4 A method for inducing endocrine tumor regression, e.g. tumor mass reduction, comprising administering to a subject in need thereof a therapeutical effective amount of an mTOR inhibitor.
- 1.5 A method for treating endocrine tumor invasiveness or symptoms associated with such tumor growth, comprising administering to a subject in need thereof a therapeutically effective amount of an mTOR inhibitor.
- 1.6 A method for preventing metastatic spread of endocrine tumors or for preventing or inhibiting growth of micrometastasis, comprising administering to a subject in need thereof a therapeutically effective amount of an mTOR inhibitor.
- 1.7 A method for the treatment of a disorder associated with endocrine tumors, comprising administering to a subject in need thereof a therapeutically effective amount of an mTOR inhibitor.
- 1.8 The use of an mTOR inhibitor for the manufacture of a medicament for use in any method of 1.1 to 1.7 above.
- 1.9 A pharmaceutical composition comprising an mTOR inhibitor in association with at least one pharmaceutically acceptable excipient, e.g. appropriate carrier and/or diluent, e.g. including fillers, binders, disintegrants, flow conditioners, lubricants, sugars or sweeteners, fragrances, preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers; for use in any method or use of 1.1 to 1.7 above.

Endocrine tumors as indicated herein e.g. include neuroendocrine tumors, e.g. including carcinoid tumors, pancreatic neuroendocrine tumors and tumors in parathyroid, pancreas, and pituitary glands.

Carcinoid tumors as indicated herein e.g. include typical and atypical carcinoids, ranging from low-grade malignant typical to intermediate atypical to high-grade large-cell neuroendocrine carcinoma and small-cell lung carcinoma; e.g. including carcinoids arising from the

foregut e.g., bronchial, pulmonary or gastric carcinoids, e.g. including primary foregut tumors confined to the thymus, lung, stomach, and duodenum; e.g. carcinoid tumors of the GI tract, e.g. located in the colon, stomach or small intestine, e.g. small-intestinal carcinoids, e.g. including

midgut, e.g., small intestine or appendiceal carcinoids, e.g. located in the distal ileum, cecum, and proximal colon,

Carcinoid lung tumors as indicated herein e.g. include neuroendocrine carcinoma, Kulchitsky cell carcinoma (KCC) (Kulchitsky cells, argentaffin cells), bronchial carcinoid tumors, bronchial adenomas, e.g. including bronchial adenomas such as a small cell carcinoma and large cell neuroendocrine tumors, typical carcinoids or atypical carcinoids associated with large bronchopulmonary carcinoid tumors or small-cell carcinomas, pulmonary carcinoids, neuroendocrine lung tumors, large-cell neuroendocrine carcinoma of the lung, (primary) pulmonary neoplasms, bronchopulmonary carcinoid tumors, lung neoplasms, lung cancers, pulmonary cancers, intrabronchial mass.

Pancreatic neuroendocrine tumors as indicated herein e.g. include islet cell tumors, APUDomas, insulinomas, glucagonomas, nonfunctioning pancreatic NETs, pancreatic NETs associated with hypercalcemia, gastrinomas, VIPomas, somatostatinomas, GRFomas.

Endocrine or neuroendocrine tumor symptoms as indicated herein e.g. include hemoptysis, cough, recurrent pulmonary infection, fever, chest discomfort and chest pain, unilateral wheezing, shortness of breath, flushing and diarrhea, endocrine or neuroendocrine syndromes carcinoid syndrome, e.g. including manifestations of either typical or atypical pulmonary carcinoid tumors, Cushing's syndrome, inappropriate secretion of ADH, increased pigmentation secondary to excess MSH, and ectopic insulin production resulting in hypoglycemia, ectopic growth hormone-releasing hormone secretion, ectopic secretion of corticotropin, cardiac manifestations secondary to fibrosis of the endocardium (endocardial fibrosis), valvular regurgitation (valvular heart disease), tricuspid insufficiency, secondary right-sided heart failure, wheezing or asthma-like symptoms, pellagra-like skin lesions with hyperkeratosis, abdominal pain, telangiectasias and paroxysmal hypotension, recurrent pneumonia, cough, chest pain.

Tumors in parathyroid, pancreas and pituitary glands as indicated herein, e.g. include pituitary tumors, nervous system tumor, such as adenomas, multiple endocrine neoplasia type 1 (MEN 1).

Pituitary tumor symptoms as indicated herein include symptoms that are associated with excess production of pituitary hormones and symptoms caused by reduced production of pituitary hormones, loss of vision, clinically nonfunctioning tumor, e.g. associated with hypopituitarism underactive pituitary gland, e.g. associated with failure of sexual function, reduced sperm production, and cessation of a woman's menstrual period, along with fatigue, prolactinoma, a benign tumor that produces the prolactin hormone, acromegaly, e.g. associated with excessive somatic growth and multiple systemic, medical consequences, Cushing's disease, nerve damage, growth disturbances, changes in hormonal balance, double or blurred vision, loss of peripheral vision, sudden blindness, headache, dizziness, loss of consciousness, nausea, weakness, unexplained weight changes, amenorrhea, erectile dysfunction in men, decreased sexual desire, especially in men, growth of skull, hands, and feet, deepening of voice, changes in facial appearance (due to changes in facial bones), wider spacing of teeth, joint pain, increased sweating, purple stretch marks on the abdomen, increased hair growth, fat deposits where the neck meets the spine, moodiness or depression, easy bruising, palpitations (rapid or irregular heartbeat), tremor, increased appetite, feeling warm or hot, difficulty falling asleep, anxiousness, frequent bowel movements, lump in the front of the neck (enlarged thyroid).

Where hereinbefore and subsequently a tumor, a tumor

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Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.