pancreatitis, cholangitis, burn injury or trauma may be more susceptible to bacterial translocation resulting in systemic inflammatory response syndrome (SIRS) or sepsis; the use of an opioid in such patients will even further increase the susceptibility to systemic inflammatory response syndrome (SIRS) or sepsis. As a consequence, opioids may not be used for pain treatment in such patients, resulting in the undertreatment of pain.

It is evident from the above that there is a need for a pharmaceutical composition, which is capable of treating pain in a patient suffering from pain and a further disease, which is negatively affecting the intestinal microbiota and/or increasing the susceptibility for intestinal bacterial translocation (resulting *inter alia* in peritonitis), wherein the pharmaceutical composition fails to have a negative impact on the intestinal microbiota and may even improve the intestinal microbiota and/or decrease the risk for intestinal bacterial translocation.

OBJECTS AND SUMMARY

The inventors surprisingly found that a pharmaceutical dosage form comprising the active agents oxycodone and naloxone is suitable for treating pain in a specific patient population, namely patients suffering from pain and a further disease, which results in intestinal dysbiosis (i.e. a further disease, which is negatively affecting the intestinal microbiota) and/or a further disease, which increases the risk for intestinal bacterial translocation (potentially leading to SIRS, sepsis and/or peritonitis).

In a first example, there is disclosed a pharmaceutical dosage form for use in the treatment of pain in patients suffering from pain and at least one further disease resulting in intestinal dysbiosis and/or a further disease, which increases the risk for peritonitis.

In a second example, there are disclosed methods of treating pain in a subject suffering from pain and at least one further disease resulting in intestinal dysbiosis and/or a further disease increasing the risk for peritonitis.

Thus, in the most preferred example, there is disclosed an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in patients suffering from i) pain and at least one further disease ii) selected from the group consisting of colorectal cancer, inflammatory bowel disease including Crohn's disease and ulcerative colitis, obesity, autism, irritable bowel syndrome, metabolic syndrome, rheumatoid arthritis, allergy, diabetes mellitus including type 2 diabetes, sepsis, Parkinson's disease, autonomic neuropathy including autonomic neuropathy in type 2 diabetes, scleroderma, achlorhydria, pancreatic exocrine insufficiency, immune-deficiency syndromes, small intestinal obstruction, diverticulitis, fistulae, surgical blind loop, previous ileo-caecal resections, post-radiation enteropathy, small intestinal pseudo-obstruction, small intestinal bacterial overgrowth syndrome, vaginal mycosis, intestinal mycosis, multiple system atrophy, food intolerance, intestinal infections, gallstones and hyperactivity of the immune system, wherein said at least one further disease ii) results in intestinal dysbiosis, and/or at least one further disease iii) selected from the group consisting of cirrhosis, hepatitis, appendicitis, pancreatitis, chronic kidney disease and cholecystitis, wherein said at least one further disease iii) increases the risk for peritonitis.

The wording used above is to be understood in the following meaning, which is to be applied throughout the present specification: an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in patients suffering from i) pain and at least one further disease ii) selected from the group consisting of colorectal cancer, inflammatory bowel disease including Crohn's

disease and ulcerative colitis, obesity, autism, irritable bowel syndrome, metabolic syndrome, rheumatoid arthritis, allergy, diabetes mellitus including type 2 diabetes, sepsis, Parkinson's disease, autonomic neuropathy including autonomic neuropathy in type 2 diabetes, scleroderma, achlorhydria, pancreatic exocrine insufficiency, immune-deficiency syndromes, small intestinal obstruction, diverticulitis, fistulae, surgical blind loop, previous ileo-caecal resections, post-radiation enteropathy, small intestinal pseudo-obstruction, small intestinal bacterial overgrowth syndrome, vaginal mycosis, intestinal mycosis, multiple system atrophy, food intolerance, intestinal infections, gallstones and hyperactivity of the immune system, wherein said at least one further disease ii) results in intestinal dysbiosis, and/or for use in the treatment of pain in patients suffering from i) pain and at least one further disease iii) selected from the group consisting of cirrhosis, hepatitis, appendicitis, pancreatitis, chronic kidney disease and cholecystitis, wherein said at least one further disease iii) increases the risk for peritonitis.

Thus, there is no link at all between disease ii) and disease iii); rather, a patient may suffer from

- i) pain and at least one further disease ii); or
- i) pain and at least one further disease iii); or
- i) pain and at least one further disease ii) and at least one further disease iii).

In other words, the presence of disease iii) is not an inevitable result of having disease ii).

In a preferred example, there is disclosed an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in patients suffering from i) pain and at least one further disease ii) selected from the group consisting of colorectal cancer, inflammatory bowel disease including Crohn's disease and ulcerative colitis, obesity, autism, irritable bowel syndrome, metabolic syndrome, rheumatoid arthritis, allergy, diabetes mellitus including type 2

diabetes, sepsis, Parkinson's disease, autonomic neuropathy including autonomic neuropathy in type 2 diabetes, scleroderma, achlorhydria, pancreatic exocrine insufficiency, immune-deficiency syndromes, small intestinal obstruction, diverticulitis, fistulae, surgical blind loop, previous ileo-caecal resections, post-radiation enteropathy, small intestinal pseudo-obstruction, small intestinal bacterial overgrowth syndrome, vaginal mycosis, intestinal mycosis, multiple system atrophy, food intolerance, intestinal infections, gallstones and hyperactivity of the immune system, wherein said at least one further disease ii) results in intestinal dysbiosis.

In another example, said at least one further disease ii) is selected from the group consisting of colorectal cancer, obesity, autism, irritable bowel syndrome, metabolic syndrome, rheumatoid arthritis, allergy, type 2 diabetes, sepsis, autonomic neuropathy in type 2 diabetes, scleroderma, achlorhydria, pancreatic exocrine insufficiency, immune-deficiency syndromes, small intestinal obstruction, diverticulitis, fistulae, surgical blind loop, previous ileo-caecal resections, post-radiation enteropathy, small intestinal pseudo-obstruction, small intestinal bacterial overgrowth syndrome, vaginal mycosis, intestinal mycosis, multiple system atrophy, food intolerance, intestinal infections, gallstones and hyperactivity of the immune system.

In another example, said at least one further disease ii) is selected from the group consisting of colorectal cancer, obesity, autism, irritable bowel syndrome, metabolic syndrome, rheumatoid arthritis, allergy, type 2 diabetes, sepsis, autonomic neuropathy in type 2 diabetes, scleroderma, achlorhydria, pancreatic exocrine insufficiency, small intestinal obstruction, diverticulitis, fistulae, previous ileo-caecal resections, post-radiation enteropathy, small intestinal pseudo-obstruction and small intestinal bacterial overgrowth syndrome.

In yet another example, said at least one further disease ii) is selected from the group consisting of colorectal cancer, obesity, autism, irritable bowel

syndrome, metabolic syndrome, sepsis and small intestinal bacterial overgrowth syndrome.

In one example, said patient is suffering from i) pain and ii) diverticulitis. In another particularly preferred embodiment, said patient is suffering from i) pain and ii) small intestinal bacterial overgrowth syndrome. In yet another particularly preferred embodiment, said patient is suffering from i) pain and ii) ulcerative colitis. In another particularly preferred embodiment, said patient is suffering from i) pain and ii) colorectal cancer.

In yet another example, the present invention relates to an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in patients suffering from i) pain and at least one further disease iii) selected from the group consisting of cirrhosis, pancreatitis, chronic kidney disease and cholecystitis, wherein said at least one further disease iii) increases the risk for peritonitis.

In yet another example, there is disclosed an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in patients suffering from i) pain and at least one further disease iii) increasing the risk for peritonitis, wherein said at least one further disease iii) is selected from the group consisting of cirrhosis, chronic kidney disease and cholecystitis. In a particularly preferred embodiment, said at least one further disease is cirrhosis.

Also disclosed herein is an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the

treatment of pain in patients suffering from i) pain and at least one further disease ii), wherein said at least one further disease ii) results in intestinal dysbiosis, or for use in the treatment of pain in patients suffering from i) pain and at least one further disease iii), wherein said at least one further disease iii) increases the risk for intestinal bacterial translocation. One may also refer to said at least one further disease iii) as increasing the risk for intestinal bacterial translocation resulting in bacteriaemia and leading to sepsis, systemic inflammatory response syndrome (SIRS) and/or peritonitis. Alternatively, one may also refer to said at least one further disease iii) as increasing the risk for intestinal bacterial translocation, wherein said bacterial translocation would then result in peritonitis, systemic inflammatory response syndrome (SIRS) and/or sepsis. In consequence, one may also refer to said at least one further disease iii) as increasing the risk for peritonitis, systemic inflammatory response syndrome (SIRS) and/or sepsis. Said at least one further disease iii), which may also be designated as disease underlying or causing the increased risk for bacterial translocation (and thus for peritonitis, systemic inflammatory response syndrome (SIRS) and/or sepsis), is preferably selected from the group consisting of trauma, burn injury, pancreatitis and cholangitis.

Specific diseases ii) resulting in intestinal dysbiosis and specific diseases iii) increasing the risk for intestinal bacterial translocation are stated below and particularly in the dependent claims of the present application.

In one example, there is disclosed an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in patients suffering from i) pain and at least one further disease ii) selected from the group consisting of diseases linked to the stomach, small intestine, colon, colon and the small intestine, and diseases generally linked to the GI tract, wherein said at least one further disease ii) results in intestinal dysbiosis. The treatment of patients suffering from i) pain and at least one further disease ii) selected from the

group consisting of diseases linked to the stomach, small intestine, colon and the small intestine, and diseases generally linked to the GI tract, wherein said at least one further disease ii) results in intestinal dysbiosis, can be preferred. Further, the treatment of patients suffering from i) pain and at least one further disease ii) selected from the group consisting of diseases linked to the stomach, small intestine, and colon and small intestine, wherein said at least one further disease ii) results in intestinal dysbiosis, is preferred. Particularly preferred is the treatment of patients suffering from i) pain and at least one further disease ii) selected from the group consisting of diseases linked to the stomach, and small intestine, wherein said at least one further disease ii) results in intestinal dysbiosis.

In another example, i) pain is not a symptom of the at least one further disease ii) and/or the at least one further disease iii) (i.e. at least one disease selected from the groups as defined above). In this embodiment, the pain is not caused by the at least one further disease ii) or the at least one further disease iii). In other words, the pain is unrelated to the at least one further disease ii) or the at least one further disease iii) and has a different origin.

In other words, another example relates to an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in patients which otherwise have to totally abstain from opioid-based pain therapy due to the presence of not opioid-induced intestinal dysbiosis as a result of at least one further disease ii) as defined above. Moreover, another example relates to an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for use in the treatment of pain in patients which otherwise have to totally abstain from opioid-based pain therapy since said patients are already at increased risk for intestinal bacterial translocation (resulting *inter alia* in peritonitis, SIRS and/or sepsis), i.e. particularly susceptible for intestinal

bacterial translocation (including susceptibility for peritonitis, SIRS and/or sepsis), as a results of at least one further disease iii) as defined above.

In another example, said intestinal dysbiosis is not induced by an opioid agonist but by said at least one further disease ii); one may also refer to said intestinal dysbiosis as being initially (i.e. prior to the treatment) not induced by an opioid agonist but by said at least one further disease ii).

In another example, said increased risk for intestinal bacterial translocation is not induced by an opioid agonist but by said at least one further disease iii); one may also refer to said increased risk for intestinal bacterial translocation as being initially (i.e. prior to the treatment) not induced by an opioid agonist but by said at least one further disease iii).

Thus, one may also refer to the above patients suffering from i) pain and the at least one further disease ii) and/or the at least one further disease iii) as defined above as opioid-naïve patients.

In a further example, said pain is moderate to severe pain.

In another example, oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof are the only pharmaceutically active agents comprised in said dosage form.

Further, a co-administration of an active agent directed to the improvement of the intestinal dysbiosis (such as e.g. probiotics) and/or of an active agent directed to the improvement of opioid-induced constipation and/or opioid-induced bowel dysfunction (such as e.g. a laxative) may not be necessary. Thus, the pain treatment regimen in a patient population suffering from i) pain and a disease ii) resulting in intestinal dysbiosis as defined above may exclude the co-administration of an active

agent directed to the improvement of the intestinal dysbiosis and/or of an active agent directed to the improvement of opioid-induced constipation and/or opioid-induced bowel dysfunction.

Also, a co-administration of an active agent decreasing the risk for intestinal bacterial translocation (such as e.g. antibiotics) and/or of an active agent directed to the improvement of opioid-induced constipation and/or opioid-induced bowel dysfunction (such as e.g. a laxative) may not be necessary. Thus, the pain treatment regimen in a patient population suffering from i) pain and a disease iii) increasing the risk for intestinal bacterial translocation as defined above may exclude the co-administration of an active agent directed at lowering the risk for intestinal bacterial translocation and/or of an active agent directed to the improvement of opioid-induced constipation and/or opioid-induced bowel dysfunction.

In another example, the dosage form comprises oxycodone or a pharmaceutically acceptable salt thereof in an amount range of equivalent to about 1 mg to about 160 mg oxycodone HCl and naloxone or a pharmaceutically acceptable salt thereof in an amount range of equivalent to about 0.5 mg to about 80 mg naloxone HCl.

The dosage form may preferably comprise oxycodone or a pharmaceutically acceptable salt thereof in an amount of equivalent to about 2.5 mg, to about 5 mg, to about 10 mg, to about 15 mg, to about 20 mg, to about 40 mg, to about 50 mg, to about 60 mg, to about 80 mg, to about 100 mg, to about 120 mg, to about 140 mg, or to about 160 mg oxycodone HCl. Naloxone or a pharmaceutically acceptable salt thereof may be present in an amount of equivalent to about 0.5 mg, to about 1 mg, to about 1.5 mg, to about 2 mg, to about 4 mg, to about 5 mg, to about 10 mg, to about 15 mg, to about 20 mg, to about 40 mg, to about 60 mg, or to about 80 mg naloxone HCl.

In yet another example, the dosage form comprises oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio range of from about 6:1 to about 1:1 (oxycodone:naloxone).

In another example, the dosage form comprises oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a 2:1 ratio by weight.

Thus, examples relate to dosage forms comprising amounts of equivalent to about 2.5 mg oxycodone HCl and about 1.25 mg naloxone HCl; about 5 mg oxycodone HCl and about 2.5 mg naloxone HCl; about 10 mg oxycodone HCl and about 5 mg naloxone HCl; about 20 mg oxycodone HCl and about 10 mg naloxone HCl; about 40 mg oxycodone HCl and about 20 mg naloxone HCl; about 80 mg oxycodone HCl and 40 mg naloxone HCl; and about 160 mg oxycodone HCl and about 80 mg naloxone HCl.

In another example, the pharmaceutically acceptable salt of the opioid agonist and/or the opioid antagonist is selected from the group comprising the hydrochloride, sulphate, bisulphate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumerate and succinate salt. It can be particularly preferred that the salt is the hydrochloride salt.

Furthermore, in another example, the dosage form may comprise further pharmaceutically acceptable ingredients and/or adjuvants, such as e.g. lubricants, fillers, binders, flowing agents, colorants, flavorants, surfactants, pH-adjusters, anti-tacking agents and/or combinations thereof.

In another example, the dosage form is a prolonged release dosage form.

It can be preferred that the prolonged release dosage form comprises a prolonged release matrix. It can further be preferred that said matrix comprises a fatty alcohol and/or a hydrophobic polymer, preferably an alkylcellulose and more preferably ethylcellulose.

It can also be preferred that the prolonged release dosage form comprises a prolonged release coating.

In a further example, the prolonged release dosage form is an osmotic prolonged release dosage form.

Further, the dosage form according to the present invention may also be an immediate release dosage form.

Preferably, the dosage form as disclosed herein is a dosage form selected from the group consisting of a tablet, a capsule, a multi-particulate, a dragée, a granulate and a powder. A particularly preferred dosage form is a tablet or a multi-particulate. Since both active agents, i.e. oxycodone and naloxone, are comprised in a single dosage form, said two active agents are not administered sequentially.

Also disclosed herein is a method of treating pain comprising administering an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof to a patient suffering from i) pain and at least one further disease ii) selected from the group consisting of colorectal cancer, inflammatory bowel disease including Crohn's disease and ulcerative colitis, obesity, autism, irritable bowel syndrome, metabolic syndrome, rheumatoid arthritis, allergy, diabetes including type 2 diabetes, sepsis, Parkinson's disease, autonomic neuropathy including autonomic neuropathy in type 2 diabetes, scleroderma, achlorhydria,

pancreatic exocrine insufficiency, immune-deficiency syndromes, small intestinal obstruction, diverticulitis, fistulae, surgical blind loop, previous ileo-caecal resections, post-radiation enteropathy, small intestinal pseudo-obstruction, small intestinal bacterial overgrowth syndrome, vaginal mycosis, intestinal mycosis, multiple system atrophy, food intolerance, intestinal infections, gallstones and hyperactivity of the immune system, wherein said at least one further disease ii) results in intestinal dysbiosis, and/or at least one further disease iii) selected from the group consisting of cirrhosis, hepatitis, appendicitis, pancreatitis, chronic kidney disease and cholecystitis, wherein said at least one further disease iii) increases the risk for peritonitis.

Also disclosed herein is a method of treating pain comprising administering an oral pharmaceutical dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof to a patient suffering from i) pain and at least one further disease ii), wherein said at least one further disease ii) results in intestinal dysbiosis, or a method of treating pain comprising administering said oral pharmaceutical dosage form to a patient suffering from i) pain and at least one further disease iii), wherein said at least one further disease iii) increases the risk for intestinal bacterial translocation.

In one aspect, the present invention refers to use of oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in the manufacture of an oral dosage form for treating pain in patients suffering from i) pain and at least one further disease ii), wherein said at least one further disease ii) results in intestinal dysbiosis, or for use in the treatment of pain in patients suffering from i) pain and at least one further disease iii), wherein said at least one further disease iii) increases the risk for intestinal bacterial translocation, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth syndrome, small

intestinal pseudo- obstruction, surgical blind loop, small intestinal obstruction, scleroderma, food intolerance, hyperactivity of the immune system, colorectal cancer, ulcerative colitis, diverticulitis, fistulae, previous ileo-caecal resection, post-radiation enteropathy, autonomic neuropathy including autonomic neuropathy in type 1 and 2 diabetes, intestinal infections, intestinal mycosis, obesity, autism, metabolic syndrome, rheumatoid arthritis, allergy, diabetes mellitus including type 2 diabetes and sepsis, and/or wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, burn injury, trauma and cholecystitis, and wherein i) pain is not a symptom of the at least one further disease ii) or the at least one further disease iii).

Also disclosed herein is method for treating pain in patients suffering from i) pain and at least one further disease ii), wherein said at least one further disease ii) results in intestinal dysbiosis, or for the treatment of pain in patients suffering from i) pain and at least one further disease iii), wherein said at least one further disease iii) increases the risk for intestinal bacterial translocation, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth syndrome, small intestinal pseudo-obstruction, surgical blind loop, small intestinal obstruction, scleroderma, food intolerance, hyperactivity of the immune system, colorectal cancer, ulcerative colitis, diverticulitis, fistulae, previous ileo-caecal resection, post-radiation enteropathy, autonomic neuropathy including autonomic neuropathy in type 1 and 2 diabetes, intestinal infections, intestinal mycosis, obesity, autism, metabolic syndrome, rheumatoid arthritis, allergy, diabetes mellitus including type 2 diabetes and sepsis, and/or wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, burn injury, trauma and cholecystitis, and wherein i) pain is not a symptom of the at least one further disease ii) or the at least one further disease iii), the method comprising the step of administering to said patient an oral dosage form comprising oxycodone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof and naloxone.

17. Use according to claim 12, wherein the dosage form comprises a prolonged release coating.

18. Use according to any one of claims 1 to 11, wherein the dosage form is an immediate release dosage form.

19. Use according to any one of the preceding claims, wherein the dosage form is a dosage form selected from the group consisting of a tablet, a capsule, a multi-particulate, a dragee, a granulate and a powder.