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(54) Title: A COMBINATION OF HYDROMORPHONE AND NALOXONE FOR USE IN TREATING PAIN IN PATIENTS SUFFERING FROM PAIN AND A DISEASE RESULTING IN INTESTINAL DYSBIOSIS AND/OR INCREASING THE RISK FOR INTESTINAL BACTERIAL TRANSLOCATION

(57) Abstract: The present invention is concerned with an oral pharmaceutical dosage form comprising hydromorphone 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 and thus for peritonitis, SIRS and/or sepsis.



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A combination of hydromorphone and naloxone for use in treating pain in patients suffering from pain and a disease resulting in intestinal dysbiosis and/or increasing the risk for intestinal bacterial translocation

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FIELD OF THE INVENTION

The present invention relates to an oral pharmaceutical dosage form comprising hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a
20 pharmaceutically acceptable salt thereof for use in the treatment of pain in patients suffering from i) pain and at least one further disease ii) resulting in intestinal dysbiosis and/or at least one further disease iii) increasing the risk for intestinal bacterial translocation resulting *inter alia* in peritonitis.

25 BACKGROUND OF THE INVENTION

It has been established over the last years that a number of diseases *inter alia* affect the intestinal microbiota. An example in this respect is colorectal cancer (Zhu et al.,
“*Gut microbiota and probiotics in colon tumorigenesis*”, Cancer Letters, 2011, Vol.
30 309, pages 119-127). Further, it is known that a number of diseases increase the susceptibility for bacterial translocation resulting *inter alia* in peritonitis, (such as e.g. cirrhosis) or in systemic inflammatory response syndrome (SIRS) or sepsis (such as e.g. pancreatitis, cholangitis, burn injury or trauma) (Gatt et al., “*Review article:*

bacterial translocation in the critically ill – evidence and methods of prevention”,
Aliment Pharmacol Ther 25, pages 741–757).

It has further been established that the intestinal microbiota plays an important role in
5 several essential processes in the human body; thus, the microbiota *inter alia*
performs a protective function, a metabolic function and a structural function. An
impaired intestinal microbiota may thus result in changes in the metabolic profile,
impairment of GI transit and pathogen overgrowth. Treatment regimens for diseases
affecting the intestinal microbiota may include the administration of probiotics in
10 order to restore or at least improve the impaired intestinal microbiota.

Patients suffering from a disease resulting in an impaired microbiota or increasing
the susceptibility for intestinal bacterial translocation may not only suffer from the
underlying disease but also from pain due to various reasons. Thus, a patient
15 suffering from colorectal cancer may also suffer from severe back pain, wherein said
back pain may have a completely different origin. The back pain may be that severe
that the patient requires a long term analgesic therapy.

Opioids correspond to the most efficient analgesics if moderate to severe pain
20 requires treatment. However, several side effect of opioid therapy are known; one of
the most prominent side effects is opioid-induced constipation, which is also
affecting the GI-tract.

If one were to treat the above mentioned patient suffering from colorectal cancer and
25 back pain with an opioid, it can be expected that the impaired microbiota will likely
not improve but, to the contrary, rather worsen. The same is true for a patient
suffering from pain and a disease, which increases the risk for intestinal bacterial
translocation; the use of an opioid in such a patient will even further increase the
susceptibility to intestinal bacterial translocation. Further, patients suffering from
30 pancreatitis, cholangitis, burn injury or trauma may be more susceptible to bacterial

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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
5 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
10 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.

15 OBJECTS AND SUMMARY OF THE INVENTION

The inventors of the present invention surprisingly found that a pharmaceutical dosage form comprising the active agents hydromorphone and naloxone is suitable for treating pain in a specific patient population, namely patients suffering from pain
20 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).

25 In a first object, the present invention is thus directed to 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.

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In a second object, the present invention is concerned with 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.

- 5 In the first object, the present invention is concerned with an oral pharmaceutical dosage form comprising hydromorphone 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
10 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.

- In the first object, the present invention in particular relates to an oral pharmaceutical
15 dosage form comprising hydromorphone 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
20 syndrome, metabolic syndrome, rheumatoid arthritis, allergy, diabetes mellitus including type 2 diabetes, sepsis, 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-
25 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,

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hepatitis, appendicitis, pancreatitis, chronic kidney disease and cholecystitis, wherein said at least one further disease iii) increases the risk for peritonitis.

In the first object, the present invention even more preferably relates to an oral
5 pharmaceutical dosage form comprising hydromorphone 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
10 bowel disease including Crohn's disease and ulcerative colitis, obesity, autism,
irritable bowel syndrome, metabolic syndrome, rheumatoid arthritis, allergy, sepsis,
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-
15 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,
20 chronic kidney disease and cholecystitis, wherein said at least one further disease iii)
increases the risk for peritonitis.

In the first object, the present invention most preferably relates to an oral
pharmaceutical dosage form comprising hydromorphone or a pharmaceutically
25 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, sepsis,
30 scleroderma, achlorhydria, pancreatic exocrine insufficiency, immune-deficiency
syndromes, small intestinal obstruction, diverticulitis, fistulae, surgical blind loop,

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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
5 disease ii) results in intestinal dysbiosis, and/or at least one further disease iii) selected from the group consisting of appendicitis, pancreatitis 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
10 applied throughout the present specification: an oral pharmaceutical dosage form comprising hydromorphone 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
15 Crohn's disease and ulcerative colitis, obesity, autism, irritable bowel syndrome, metabolic syndrome, rheumatoid arthritis, allergy, diabetes mellitus including type 2 diabetes, sepsis, autonomic neuropathy including autonomic neuropathy in type 2 diabetes, scleroderma, achlorhydria, pancreatic exocrine insufficiency, immune-deficiency syndromes, small intestinal obstruction, diverticulitis, fistulae, surgical
20 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
25 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.

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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

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

5 - 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).

It is to be understood that the pharmaceutical dosage forms of the invention are
10 suitable for use in the treatment of pain in a patient group suffering from i) pain and
at least one further disease ii) and/or iii). In this connection, it is to be understood
that the pain is treated, but not necessarily the at least one further disease ii) and/or
iii) itself. Rather, as regards the at least one further disease ii) and/or iii), it is to be
understood that the results of these diseases, namely intestinal dysbiosis and an
15 increased risk for intestinal bacterial translocation (referred to in the following as
“intestinal problems”), are at least not further worsened or even alleviated upon
administration of the dosage form of the present invention. Furthermore, the pain is
typically not a symptom of the disease ii) or iii). Due to the fact that the patient
suffers not only from pain but also from at least one further disease ii) and/or iii), the
20 patient’s pain would typically not be treated with opioids for the reason that the
diseases ii) and/or iii) are typically accompanied by the above-mentioned intestinal
problems. However, it has surprisingly been found that the dosage forms of the
present invention are suitable for use in the treatment of pain in these patients
without increasing these intestinal problems or even decreasing these intestinal
25 problems. Thus, although the diseases ii) and/or iii) themselves are not necessarily
treated by the dosage forms of the invention, pain in patients suffering from these
diseases may advantageously be treated, as the symptoms of intestinal dysbiosis
and/or an increased intestinal bacterial translocation risk (referred to above as
“results” of these diseases), which are associated with these diseases, are not
30 deteriorated as one would expect, but may even be positively influenced.

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In an embodiment, the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone 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, 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 appendicitis, pancreatitis and cholecystitis, wherein said at least one further disease iii) increases the risk for peritonitis.

In a preferred embodiment, the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone 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, sepsis, 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 appendicitis, pancreatitis and cholecystitis, wherein said at least one further disease iii) increases the risk for peritonitis.

In another preferred embodiment, the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone 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, 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 preferred embodiment, the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone 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, sepsis,

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- 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,
- 5 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 preferred embodiment, said at least one further disease ii) is selected from
- 10 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-
- 15 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.

- 20 In another preferred embodiment, 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, sepsis, scleroderma, achlorhydria, pancreatic exocrine insufficiency, immune-deficiency syndromes, small intestinal obstruction, diverticulitis, fistulae, surgical blind loop, previous ileo-caecal
- 25 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 preferred embodiment, 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

5 insufficiency, small intestinal obstruction, diverticulitis, fistulae, previous ileo-caecal resections, post-radiation enteropathy, small intestinal pseudo-obstruction and small intestinal bacterial overgrowth syndrome.

In another preferred embodiment, said at least one further disease ii) is selected from
10 the group consisting of colorectal cancer, obesity, autism, irritable bowel syndrome, metabolic syndrome, rheumatoid arthritis, allergy, sepsis, 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.

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In yet another preferred embodiment, 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.

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In a particularly preferred embodiment, 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)
25 ulcerative colitis. In another particularly preferred embodiment, said patient is suffering from i) pain and ii) colorectal cancer.

In yet another preferred embodiment, the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone or a pharmaceutically
30 acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for

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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 pancreatitis and cholecystitis, wherein said at least one further disease iii) increases the risk for peritonitis.

- 5 In yet another preferred embodiment, the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone 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
10 iii) is selected from the group consisting of cirrhosis, chronic kidney disease and cholecystitis.

- In yet another preferred embodiment, the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone or a pharmaceutically
15 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 cholecystitis.

- 20 The present invention is in particular directed in the first object to an oral pharmaceutical dosage form comprising hydromorphone 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,
25 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
30 (SIRS) and/or peritonitis. Alternatively, one may also refer to said at least one further

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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
5 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, more
10 preferably from trauma, 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.

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In a preferred embodiment, the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone 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)
20 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,
25 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
30

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.

- 5 In a particularly preferred embodiment, 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.
- 10

- In other words, another embodiment of the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof for
- 15 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 embodiment of the present invention relates to an oral pharmaceutical dosage form comprising hydromorphone or a pharmaceutically acceptable salt thereof and
- 20 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
- 25 peritonitis, SIRS and/or sepsis), as a results of at least one further disease iii) as defined above.

In another preferred embodiment, 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

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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).

5 In another preferred embodiment, 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).

10 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 preferred embodiment, said pain is moderate to severe pain.

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In another preferred embodiment, hydromorphone 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.

20 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
25 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
5 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.

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In another preferred embodiment, the dosage form comprises hydromorphone or a pharmaceutically acceptable salt thereof in an amount range of equivalent to about 1 mg to about 64 mg hydromorphone HCl and naloxone or a pharmaceutically acceptable salt thereof in an amount range of equivalent to about 1 mg to about 256
15 mg naloxone HCl.

The dosage form may preferably comprise hydromorphone or a pharmaceutically acceptable salt thereof in an amount of equivalent to about 1 mg, to about 2 mg, to about 4 mg, to about 8 mg, to about 12 mg, to about 16 mg, to about 24 mg, to about
20 32 mg, to about 40 mg, to about 48 mg or to about 64 mg hydromorphone HCl. Naloxone or a pharmaceutically acceptable salt thereof may be present in an amount of equivalent to about 1 mg, to about 2 mg, to about 4 mg, to about 8 mg, to about 12 mg, to about 16 mg, to about 24 mg, to about 32 mg, to about 48 mg, to about 64 mg, to about 96 mg, to about 128 mg or to about 256 mg naloxone HCl.

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In yet another preferred embodiment, the dosage form comprises hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio range corresponding to about 2:1 to about 1:3 (hydromorphone HCl:naloxone HCl). In yet another preferred embodiment, the
30 dosage form comprises hydromorphone or a pharmaceutically acceptable salt thereof

and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio range corresponding to about 2:1 to about 1:2 (hydromorphone HCl:naloxone HCl).

5 In a preferred embodiment, the dosage form comprises hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio corresponding to about 2:1 or 1:1 or 1:2 or 1:3 of hydromorphone HCl:naloxone HCl.

10 In a particularly preferred embodiment, the dosage form comprises hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio corresponding to about 1:2 of hydromorphone HCl:naloxone HCl. Thus, preferred embodiments relate to dosage forms comprising amounts of equivalent to about 1 mg hydromorphone HCl and about 2 mg naloxone HCl; about 2 mg hydromorphone HCl and about 4 mg
15 naloxone HCl; about 4 mg hydromorphone HCl and about 8 mg naloxone HCl; about 8 mg hydromorphone HCl and about 16 mg naloxone HCl; about 16 mg hydromorphone HCl and about 32 mg naloxone HCl; about 24 mg hydromorphone HCl and about 48 mg naloxone HCl; about 32 mg hydromorphone HCl and about 64 mg naloxone HCl; about 40 mg hydromorphone HCl and about 80 mg naloxone HCl;
20 about 48 mg hydromorphone HCl and about 96 mg naloxone HCl; and about 64 mg hydromorphone HCl and about 128 mg naloxone HCl.

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

Furthermore, in an also preferred embodiment, the dosage form may comprise
30 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.

5 In another preferred embodiment, 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 prolonged release matrix comprises a prolonged release material selected from the group consisting of
10 hydrophobic or hydrophilic polymers, protein-derived material, gums, substituted or unsubstituted hydrocarbons, digestible carbohydrates, fatty acids, fatty alcohols, glyceryl esters of fatty acids, natural and synthetic oils and natural and synthetic waxes.

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

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

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

Preferably, the dosage form according to the present invention is a dosage form
25 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. hydromorphone and naloxone, are comprised in a single dosage form, said two active agents are not administered sequentially.

30

In the second object, the present invention is concerned with a method of treating pain comprising administering an oral pharmaceutical dosage form comprising hydromorphone 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.

10

In the second object, the present invention is in particular concerned with a method of treating pain comprising administering an oral pharmaceutical dosage form comprising hydromorphone 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, 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.

30

In the second object, the present invention is even more preferably concerned with a method of treating pain comprising administering an oral pharmaceutical dosage form comprising hydromorphone 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, sepsis, 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.

In the second object, the present invention is most preferably concerned with a method of treating pain comprising administering an oral pharmaceutical dosage form comprising hydromorphone 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, sepsis, 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,

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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 appendicitis, pancreatitis and cholecystitis, wherein said at least one further disease
5 iii) increases the risk for peritonitis.

All embodiments mentioned above for the first object also apply for the second object of the present invention.

10 DESCRIPTION OF THE FIGURES

Figure 1 depicts a graphic of the study design of Example 1.

Figure 2 depicts the study design of Example 2.

15

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention *inter alia* succeeded in providing a pharmaceutical dosage form for use in the treatment of pain in patients suffering from i) pain and at least one further disease ii), e.g. as defined herein, resulting in
20 intestinal dysbiosis. Further, the inventors were successful in providing a pharmaceutical dosage form, which can be used for pain treatment in patients suffering from i) pain and are particularly susceptible for intestinal bacterial translocation (and thus e.g. peritonitis, SIRS and/or sepsis), e.g. due to at least one
25 further disease iii) as defined herein.

Before some of the embodiments of the present invention are described in more detail, the following definitions are introduced.

30 DEFINITIONS

As used in the specification and the claims, the singular forms of “a” and “an” also include the corresponding plurals unless the context clearly dictates otherwise.

- 5 The term “about” in the context of the present invention denotes an interval of accuracy that a person skilled in the art will understand to still ensure the technical effect of the feature in question. The term typically indicates a deviation from the indicated numerical value of $\pm 10\%$ and preferably $\pm 5\%$.
- 10 It needs to be understood that the term “comprising” is not limiting. For the purposes of the present invention, the term “consisting of” is considered to be a preferred embodiment of the term “comprising”. If hereinafter a group is defined to comprise at least a certain number of embodiments, this is also meant to encompass a group which preferably consists of these embodiments only.
- 15 “Treatment of pain” is to be understood as referring to a general improvement or even cure of the patient’s pain or to the alleviation of pain. Such an improvement/cure or alleviation can either be detected by the patient’s subjective feeling or by external observations. The intensity of pain may e.g. be assessed using a pain
- 20 intensity scale; this scale may refer to the average pain over the last 24 hours (Scale of 0 – 10, 0=no pain; 10=strong pain).

The term “microbiota” is interchangeably used herein with the terms “microbiome” and “(micro)flora” and refers to the totality of microbial cells in the human body,

25 wherein the present invention has a particular focus on the totality of microbial cells in the GI tract or gut. The GI tract is inhabited with 10^{13} to 10^{14} microorganisms (thought to be 10 times that of the number of human cells in the body and 100 times as many genes as the human genome). The estimated species number varies greatly but it is generally accepted that the adult microbiota consists of greater than 1000

30 species and more than 700 strains. It is an environment dominated by bacteria,

mainly strict anaerobes, but also including viruses, protozoa, archaea and fungi (see introductory part of Grenham et al., “*Brain-gut-microbe communication in health and disease*”, Frontiers in physiology, 2011, Vol. 2, Article 94, for further details).

- 5 The term “intestinal dysbiosis” means an impaired or altered intestinal microbiota. It may also be described as a shift in the makeup of the commensal microflora to a nonphysiologic composition. This may e.g. mean that obligate bacteria, *Bifidobacteria*, *Lactobacilli* and *E.coli* (apathogenic) are reduced relative to the normal intestinal microflora, wherein obligate bacteria may partly disappear and
- 10 *Bifidobacteria* are reduced or almost disappear. Aerobes and *Bacterioids*, *Clostridia*, *Streptococci*, *P. aeruginosa* and other pathogenic bacteria, fungi, mould, lactose-negative enterobacteria and *E.coli* (pathogenic) may be increased relative to the normal intestinal microflora. In Wikipedia, the term “dysbiosis” is defined as follows: “Dysbiosis (also called “dysbacteriosis”) refers to microbial imbalance on or
- 15 inside the body. Dysbiosis is most commonly reported as a condition in the digestive tract. It has been associated with illnesses, such as inflammatory bowel disease, chronic fatigue syndrome, obesity, cancer and colitis. Microbial colonies found on or in the body are normally benign or beneficial. These beneficial and appropriately sized microbial colonies carry out a series of helpful and necessary functions, such as
- 20 aiding in digestion. They also protect the body from the penetration of pathogenic microbes. These beneficial microbial colonies compete with each other for space and resources and outnumber human cells by a factor 10:1. The term "dysbiosis" is not a standardized medical term. Apparently similar concepts are also described as "microbial imbalance", "bacterial imbalance", or "increased levels of harmful
- 25 bacteria and reduced levels of the beneficial bacteria".

- “Peritonitis” is used herein in its general meaning, i.e. as corresponding to an inflammation of the peritoneum. “Systemic inflammatory response syndrome (SIRS)” and “sepsis” are used herein in the general meaning, i.e. that SIRS is a
- 30 clinical syndrome that complicates a noninfectious insult (e.g., acute pancreatitis,

pulmonary contusion) and sepsis a clinical syndrome that complicates severe infection, respectively. The patient population suffering from at least one disease as listed herein under disease iii) is particularly vulnerable to developing peritonitis, SIRS and/or sepsis. This means that the patient is not actually suffering from

5 peritonitis, SIRS and/or sepsis but at a higher risk of developing peritonitis, SIRS and/or sepsis than a patient not suffering from at least one of the disease as listed herein under disease iii). The term “risk” and “susceptibility” are used interchangeably herein; “increased risk” or “increased susceptibility” means that patients are prone to a specific disease. The term “increases the risk for peritonitis”

10 may also be understood as “results in a pre-condition of peritonitis” or as “makes the patient susceptible for peritonitis”. The term “increases the risk for systemic inflammatory response syndrome (SIRS)” or “sepsis” may also be understood as “results in a pre-condition of SIRS or sepsis” or as “makes the patient susceptible for SIRS or sepsis”.

15

The term “intestinal bacterial translocation” as used herein means that live bacteria and/or its products cross the intestinal barrier. Such a translocation will in almost all cases result in infectious complications. As noted above, specific diseases resulting from an intestinal bacterial translocation are peritonitis, SIRS and sepsis. Thus, the

20 term “increases the risk for intestinal bacterial translocation” may also be understood as “results in a pre-condition of peritonitis, SIRS and/or sepsis” or “makes the patient susceptible for peritonitis, SIRS and/or sepsis”.

It is to be understood that “intestinal dysbiosis” and “intestinal bacterial

25 translocation” are symptoms/results, which typically accompany the diseases ii) and iii) as defined herein. Thus, the at least one disease ii) as defined herein is typically accompanied by intestinal dysbiosis, which is indicated by the definition that the disease ii) “results in intestinal dysbiosis”. On the other hand, the at least one disease iii) as defined herein is typically accompanied by an increased risk for intestinal

30 bacterial translocation, which is indicated by the definition that the disease iii)

- 25 -

“increases the risk for intestinal bacterial translocation”, in particular the risk for peritonitis. This is set out in more detail on pages 26 to 33 of the present application when describing the patient population.

- 5 The term “opioid-naïve patient” means that the patient has not recently taken an opioid on a regular basis.

The term “probiotics” refers to live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host.

10

“Hyperactivity of the immune system” as used herein comprises one or more of the following: increase of CD3+, CD4+, CD8+ T-cells and activated CD25+, spontaneous proliferation of lymphocytes and increased titer of certain anti-bacterial antibodies, e.g. *E.coli* and *S. aureus* antibodies, increased values of IgA and IgM to
15 gram negative enterobacteria or their endotoxins such as *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Proteus mirabilis*, *Pseudomonas putida*, *Citrobacter koseri* and/or *Klebsiella pneumoniae*.

In the context of the present invention, the term “prolonged release” refers to
20 pharmaceutical dosage forms showing a slower release of the active agents than that of a conventional release pharmaceutical dosage forms administered by the same route. Prolonged release is achieved by a special formulation design and/or manufacturing method. In general, “prolonged release dosage forms” in the context of the present invention means that hydromorphone and naloxone are released from
25 the pharmaceutical dosage form over an extended period of time.

The term “immediate release” as used herein refers to pharmaceutical dosage forms showing a release of the active substances which is not deliberately modified by a special formulation design and/or manufacturing methods.

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“Pharmaceutically acceptable salts” include, but are not limited to, inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, malate, maleate, tartrate, bitartrate, fumarate, succinate, citrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparagine, glutamate and the like, and metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like.

DETAILED DESCRIPTION OF THE PATIENT POPULATION AND THE ORAL DOSAGE FORM

The oral pharmaceutical dosage form according to the present invention is intended for treatment of pain in a patient population suffering from i) pain and ii) at least one further disease resulting in intestinal dysbiosis and/or iii) at least one further disease increasing the risk for intestinal bacterial translocation.

A link to intestinal dysbiosis has been established for the following diseases: colorectal cancer (see e.g. Azcarate-Peril et al., “*The intestinal microbiota, gastrointestinal environment and colorectal cancer: a putative role for probiotics in prevention of colorectal cancer?*”, Am J Physiol Gastrointest Liver Physiol, 2011, Vol. 301, No. 3, G401-24; Zhu et al., “*Gut microbiota and probiotics in colon tumorigenesis*”, Cancer Letters, 2011, Vol. 309, pages 119-127), inflammatory bowel disease including Crohn’s disease and ulcerative colitis (see e.g. Salzmann and Bevins “*Negative interactions with the microbiota: IBD*”, Adv Exp Med Biol, 2008, Vol. 635, pages 67-78; Rausch et al., “*Colonic mucosa-associated microbiota is influenced by an interaction of Crohn’s disease and FUT2 (Secretor) genotype*”, 2011, Vol. 108, No. 47, pages 19030-5), obesity (see e.g. Ley et al., “*Obesity alters*

gut microbial ecology", PNAS, 2005, Vol. 102, No. 31, pages 11070-11075), autism (see e.g. Grenham et al., "*Brain-gut-microbe communication in health and disease*", *Frontiers in physiology*, 2011, Vol. 2, Article 94), irritable bowel syndrome (see e.g. O Noor et al., "*Ulcerative colitis and irritable bowel patients exhibit distinct abnormalities of the gut and microbiota*", *Gastroenterology*, 2010, Vol. 10, No. 134; Ponnusamy et al., "*Microbial Community and metabolomic comparison of irritable bowel syndrome faeces*", *Journ Med Microbiol*, 2011, Vol. 60, pages 817-827), metabolic syndrome (see e.g. Zhu et al., "*Gut microbiota and probiotics in colon tumorigenesis*", *Cancer Letters*, 2011, Vol. 309, pages 119-127), rheumatoid arthritis (see e.g. Scher and Abramson, "*The microbiome and rheumatoid arthritis*", *Nat Rev Rheumatol.*, 2011, Vol. 7, No. 10, Pages 569-578), allergy (see e.g. Shreiner et al., "*The 'microflora hypothesis' of allergic disease*", *Adv Exp Med Bio*, 2008, Vol. 635, pages 113-134), diabetes including type 2 diabetes (see e.g. Larsen et al., "*Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults*" PLOS ONE, 2010 (February), Vol. 5, No. 2), sepsis (see e.g. Harari et al., "*The effect of morphine on mast cell-mediated mucosal permeability*", 2006, *Surgery*, Vol. 139, No. 1, pages 54-60; Runkel et al., "*Alterations in rat intestinal transit by morphine promote bacterial translocation*", *Dig Diseases and Sciences*, 1993, Vol. 38, No. 8, pages 1530-1536), 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 (see e.g. Kopacova, "*Small intestinal bacterial overgrowth syndrome*", 2010, Vol. 16, No. 24, pages 2978-2990 and Quigley EM and Abu-Shanab A, "*Small intestinal bacterial overgrowth*", *Infect Dis Clin North Am*, 2010, Vol. 24, No. 4, pages 943-59), autonomic neuropathy including autonomic neuropathy in type 2 diabetes (see e.g. Bures et al., "*small intestinal bacterial overgrowth syndrome*", 2010, *World J Gastroenterol*, Vol. 16, No. 24, pages 2978-2990), vaginal mycosis and intestinal mycosis (see e.g. Achkar and Fries, "*Candida infections of the genitourinary tract*", 2010, *clinical microbiology reviews*, Vol. 23, pages 253-273), multiple system

atrophy, food intolerance, intestinal infections, gallstones and hyperactivity of the immune system.

As mentioned below, dysbiosis is known to affect the upper and mid GI tract including the stomach, the small intestine and the colon. If classified according to the region in the GI tract, achlorhydria is linked to dysbiosis in the stomach, whereas the following diseases are linked to dysbiosis in the small intestine: pancreatic exocrine insufficiency, small intestinal bacterial overgrowth syndrome, small intestinal pseudo-obstruction, surgical blind loop, small intestinal obstruction, scleroderma, food intolerance and hyperactivity of the immune system. The following diseases are linked to dysbiosis in the colon: colorectal cancer, ulcerative colitis, diverticulitis, and fistulae, whereas the following diseases are linked to dysbiosis in the colon and the small intestine: Crohn's disease, previous ileo-caecal resection, post-radiation enteropathy, autonomic neuropathy including autonomic neuropathy in type 1 and 2 diabetes, intestinal infections and intestinal mycosis. The following diseases are also linked to dysbiosis, wherein there appears to be no link to a specific region in the GI tract: obesity, autism, metabolic syndrome, rheumatoid arthritis, allergy, diabetes mellitus including type 2 diabetes and sepsis.

Thus, intestinal dysbiosis is present in the above mentioned patient population suffering from i) pain and ii) at least one further disease selected from the diseases outlined above.

The intestinal microbiota carries out important effects such as protective, structural and metabolic effects on the intestinal mucosa. The main functions appear to be the following: a protective function (pathogen displacement, nutrient competition, receptor competition, production of anti-microbial factors), a structural function (barrier fortification, induction of IgA, apical tightening of tight junctions, immune system development) and a metabolic function (control of epithelial cell differentiation and proliferation, metabolism of dietary carcinogens, synthesis of

vitamins, fermentation of non-digestible dietary residue and epithelial-derived mucus, iron absorption, salvage of energy).

Intestinal dysbiosis therefore results in an impairment or even complete loss of the
5 above functions and may particularly manifest in changes in the metabolic profile, gas production, impairment of GI transit, epithelial barrier dysfunction, pathogen overgrowth and mucosal immune equilibrium changes.

A patient suffering from at least one disease iii) as defined above is particularly
10 susceptible for increased intestinal bacterial translocation and thus developing peritonitis, SIRS and/or sepsis. Generally, patients with an impaired liver function, e.g. due to cirrhosis or hepatitis, particularly hepatitis B and C, are at higher risk for an increased intestinal bacterial translocation and thus e.g. for peritonitis. This is also the case for patients suffering from chronic kidney disease. A particular patient
15 population being at increased risk for an increased intestinal bacterial translocation and thus e.g. for peritonitis corresponds to patients undergoing peritoneal dialysis, e.g. as a treatment form of chronic kidney disease. Also, patients suffering from an infection in a specific organ, which may spread, are at higher risk for increased intestinal bacterial translocation resulting in peritonitis, SIRS and/or sepsis. Such
20 patients may e.g. suffer from appendicitis, pancreatitis, and cholecystitis. It should be noted that patients suffering from Crohn's disease and diverticulitis, which are listed above under diseases resulting in intestinal dysbiosis, may also be at increased risk for increased intestinal bacterial translocation and thus e.g. may develop peritonitis, SIRS and/or sepsis.

25

Patients suffering from at least one disease iii) are thus particularly vulnerable to increased bacterial translocation and even a low number of bacterial translocation may suffice to actually induce peritonitis, SIRS and/or sepsis. If such a patient additionally suffers from pain, a pain treatment should be selected, which fails to

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further increase the risk of peritonitis, SIRS and/or sepsis, e.g. by inducing an increased bacterial translocation.

Efficient pain treatment, particularly treatment of moderate to severe pain, can
5 generally be achieved by the administration of opioid analgesics, such as e.g. morphine or hydromorphone. However, the administration of opioid analgesics may result in undesirable side effects, including undesirable side effects in the GI tract. Particularly prominent side effects are opioid-induced constipation (OIC) and opioid-induced bowel dysfunction (OIBD). Further, as *inter alia* shown herein, the
10 administration of opioid analgesics also negatively affects the intestinal microbiota and results in an increased bacterial translocation.

It is important to note that no correlation or link between OIC or non-opioid induced constipation and intestinal dysbiosis has been established thus far. This is *inter alia*
15 confirmed e.g. by the definition of the term “dysbiosis” in Wikipedia as recited above, wherein no link between constipation and dysbiosis is made. Rather, constipation is known as developing in the lower GI tract (the colon) only, whereas dysbiosis also affects the upper and mid GI tract including the stomach. Thus, e.g. achlorhydria linked to dysbiosis in the stomach or e.g. pancreatic exocrine
20 insufficiency or small intestinal bacterial overgrowth syndrome linked to dysbiosis in the small intestine are completely unrelated to constipation and no conclusion or transfer can be made from constipation in the colon to any of these diseases. Further, it appears that constipation is not a precondition for intestinal dysbiosis; to the contrary, intestinal dysbiosis may be present without any constipation or even cause
25 constipation.

Since OIC corresponds to a well-known side effect of opioid analgesic therapy, a physician confronted with the above mentioned patient population (in which intestinal dysbiosis is present and/or which is particularly vulnerable to bacterial
30 translocation), will likely be reluctant to administer an active agent, for which a

further worsening of a GI parameter, namely constipation, is known. Moreover, opioid analgesic therapy has a further negative impact on the intestinal dysbiosis and increases the risk for bacterial translocation, as shown in the present application and as discussed in the next paragraphs. In consequence, this will result in the

5 undertreatment of pain in such patients since a physician is reluctant to prescribe the administration of e.g. hydromorphone alone.

Alternatively, if the physician decides to administer an opioid analgesic in order to treat pain, the additional administration of an active agent alleviating the intestinal

10 dysbiosis appears advisable in order to preemptively counter the further worsening of GI parameters. Such an additional therapy may reside in the administration of probiotics such as e.g. lactic acid bacteria or *Bifidobacteria* to improve dysbiosis. In case of a pain patient being particularly susceptible for peritonitis, the additional administration of an active agent decreasing this susceptibility appears advisable in

15 order to preemptively address a possible peritonitis. Such an additional therapy may reside in the administration of antibiotics. Furthermore, it might even be advisable under the above circumstances to administer an active agent symptomatically counteracting the OIC, such as e.g. a laxative.

20 Clearly, either the undertreatment of pain or the additional administration of further active agents, which cause further side effects and additional direct or indirect costs (e.g. to treat or manage side effects, costs of additional medication) next to the opioid analgesic is undesirable.

25 The present inventors have now surprisingly found that the administration of a combination of the opioid agonist hydromorphone and the opioid antagonist naloxone solves the above problem. Thus, the combination is not only effective in counteracting the side effect OIC while maintaining analgesia without any substantial loss in the actual analgesia, but is also suitable for improving intestinal

30 dysbiosis or at least not further worsening intestinal dysbiosis. This is achieved by

the presence of naloxone in the combination, which has a positive effect particularly on the intestinal microbiome and results in a restored intestinal barrier function.

- 5 The actual treatment of pain with a combination of hydromorphone and naloxone is thus possible in the patient population with intestinal dysbiosis while the intestinal dysbiosis may even be improved or at least not further worsened; accordingly, the administration of additional active agents would be unnecessary with respect to the improvement of intestinal dysbiosis or OIC. A corresponding pain treatment regimen in the patient population as set out above may thus rely on the administration of a
- 10 dosage form comprising hydromorphone and naloxone only. The combination may also particularly be used in pain patients with an increased susceptibility for peritonitis, SIRS and/or sepsis as a prophylactic measure against an actual peritonitis, SIRS and/or sepsis. The administration of additional prophylactic active agents such as antibiotics would thus be unnecessary with respect to the prophylaxis of
- 15 peritonitis, SIRS and/or sepsis if a combination of hydromorphone and naloxone is administered. Pain treatment in a patient population suffering from pain and having an increased risk for intestinal bacterial translocation may thus rely on the administration of a dosage form comprising hydromorphone and naloxone only.
- 20 More generally, one may thus refer to pain treatment by the combination of hydromorphone and naloxone as efficient pain management while improving GI parameters; this not only refers to GI parameters in the lower GI tract, such as e.g. OIC, but also to GI parameters in the upper and mid GI tract (including the stomach and the small intestine), such as e.g. intestinal dysbiosis or an increased risk of
- 25 bacterial translocation. An analysis of GI parameters in the upper and mid GI tract may *inter alia* be carried out by a quantitative analysis of intestinal microbiota, the oro-caecal transit time, bacterial translocation and gastric emptying or parameters such as e.g. the intestinal and serum metabolome, the abdominal girth, stool consistency (using the Bristol Stool Form Scale), immune and inflammatory

responses, and correlations between said parameters. For correlation reasons, the analysis of parameters of the lower GI tract, such as e.g. OIC, may be included.

One may thus refer to the combination of hydromorphone and naloxone as being
5 suitable for the treatment of pain while not only improving OIC (and consequences of OIC such as hemorrhoids or hemorrhoidal bleeding) but also opioid-induced bowel dysfunction in the upper and mid GI tract. Opioid-induced bowel dysfunction may also be referred to as “GI dysfunction”.

10 RELEASE BEHAVIOR OF THE DOSAGE FORM

In general, the release behavior of a dosage form can *inter alia* be determined by an *in vitro* release test.

15 In this regard, the term “*in vitro* release” refers to the release rate at which a pharmaceutically active agent, e.g. hydromorphone HCl, is released from the pharmaceutical composition when the *in vitro* release rate is tested by the paddle method according to the European Pharmacopeia as described in the Ph. Eur. 2.9.3
6th edition. The paddle speed is set at 100 rpm in simulated gastric fluid (SGF)
20 dissolution medium with pH 1.2. Aliquots of the dissolution media are withdrawn at the respective time points and analyzed by HPLC with a C18 column, eluted with 30mM phosphate buffer in acetonitrile (70:70; pH 2.9) with a flow rate of 1.0 ml/min and detected at 220 nm. The term “Simulated Gastric Fluid, pH 1.2” refers to 0.1 N HCl, pH 1.2.

25

In contrast to an “immediate release”, a “prolonged release” dosage form in accordance with the present invention refers to pharmaceutical compositions which release *in vitro* $\leq 75\%$ (by weight) of the pharmaceutically active agents, namely hydromorphone and naloxone, at 45 min.

30

In the context of the present invention, the term “immediate release” refers to pharmaceutical compositions showing a release of the active substance(s) which is not deliberately modified by a special formulation design and/or manufacturing methods. For oral dosage forms this means that the dissolution profile of the active substance(s) depends essentially on its (theirs) intrinsic properties. Typically, the term “immediate release” refers to pharmaceutical compositions which release *in vitro* >75% (by weight) of the pharmaceutically active agent(s) at 45 min.

Prolonged release properties may be obtained by different means such as by a coating which is then designated as a prolonged release coating, a matrix which is then designated as a prolonged release matrix or e.g. by an osmotic structure of the pharmaceutical composition.

In order to obtain “prolonged release” properties, one typically uses materials which are known to prolong the release from a dosage form comprising e.g. a prolonged release matrix and/or prolonged release coating. Typical examples are set out further below. The nature of the “prolonged release material” may depend on whether the release properties are attained by a “prolonged release matrix” or a “prolonged release coating”. The term “prolonged release materials” thus describes both types of materials. The term “prolonged release matrix material” indicates that a material is used for obtaining a prolonged release matrix. Likewise, the term “prolonged release coating material” indicate that a material is used for obtaining a prolonged release coating.

The term “prolonged release matrix formulation” refers to a pharmaceutical composition including at least one prolonged release material, and at least hydromorphone and naloxone as the two pharmaceutically active agents. In a “prolonged release matrix formulation”, the “prolonged release materials” are combined with the pharmaceutically active agents to form a mixture from which the

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pharmaceutically active agents are released over prolonged periods of time, such as e.g. 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours.

5 It is to be understood that a material will be considered to act as prolonged release material if the dissolution profile of the pharmaceutically active agents is slowed down compared to an immediate or conventional release formulation. If a prolonged release material can be used for manufacturing a prolonged release matrix, it will be considered as a prolonged release matrix material.

10 Pharmaceutically acceptable excipients which are used to adjust an already prolonged release to a specific profile are not necessarily considered to be prolonged release materials.

15 It is to be understood that a prolonged release matrix does not necessarily consist only of the pharmaceutically active agents and the prolonged release material. The prolonged release matrix may comprise in addition pharmaceutically acceptable excipients such as fillers, lubricants, glidants, etc. Examples of such excipients are set out below.

20 The term “prolonged release coating formulation” refers to a pharmaceutical composition including at least one prolonged release material, and hydromorphone and naloxone as the two pharmaceutically active agents. In a “prolonged release coating formulation”, the “prolonged release materials” are disposed on the pharmaceutically active agents to form a diffusion barrier. Other than in prolonged
25 release matrix formulation, the actives are not intimately mixed with the prolonged release material and the prolonged release coating does not form a three dimensional structure within which the actives are distributed. As the term implies, the prolonged release material forms a layer above the actives. The pharmaceutically active agents are released from a prolonged release coating formulation over prolonged periods of
30 time, such as e.g. 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours.

It is to be understood that a material will be considered to act as prolonged release material if the dissolution profile of the pharmaceutically active agents is slowed down compared to an immediate or conventional release formulation. If a prolonged
5 release material can be used for manufacturing a prolonged release coating, it will be considered as a prolonged release coating material.

Pharmaceutically acceptable excipients which are used to adjust an already prolonged release to a specific profile are not necessarily considered to be prolonged
10 release materials.

When it is mentioned that a prolonged release coating is disposed on pharmaceutically active agents, this is not to be construed as meaning that such a coating will necessarily be directly layered on such active pharmaceutically agents.
15 Of course, if the pharmaceutically active agents hydromorphone and naloxone are layered on a carries such as nu-Pareil beads, the coating may be disposed directly thereon. However, the pharmaceutically active agents may also be first embedded in a polymer layer or e.g. a prolonged release matrix. Subsequently the prolonged release coating may be disposed on e.g. granules which comprise a prolonged release
20 matrix or on tablets which are made from such granules by compression for example.

A pharmaceutical composition with a prolonged release coating may be obtained by combining the pharmaceutically active agents with a carries such as non-Pareil beads and disposing a prolonged release coating on said combinations. Such coating may
25 be made from polymers such cellulose ethers with ethyl cellulose being preferred, acrylic resins, other polymers and mixtures thereof. Such prolonged release coatings may comprise additional excipients such as pore-formers, binders and the like.

It is further to be understood, that the term "prolonged release matrix formulation"
30 does not exclude pharmaceutical compositions with a prolonged release matrix and

an additional prolonged release coating being disposed on the matrix. Likewise the term “prolonged release coating formulation” does not exclude pharmaceutical compositions with a prolonged release coating which is disposed on prolonged release matrix.

5

The term “prolonged release dosage form” refers to the administration form of a pharmaceutical composition of the present invention comprising the two pharmaceutically active agents, i.e. hydromorphone and naloxone, in prolonged release form as e.g. in form of a “prolonged release matrix formulation”, in the form
10 of a “prolonged release coating formulation”, combinations thereof or in other prolonged release formulations such as osmotic formulations. The terms “prolonged release matrix formulation” and “prolonged release dosage form” can be used interchangeably if the prolonged release dosage form consists essentially of the prolonged release matrix formulation. This means that a prolonged release dosage
15 form can comprise in addition to the prolonged release matrix e.g. cosmetic coatings and pharmaceutically acceptable excipients such fillers, lubricants, etc.

For some embodiments, the term “prolonged release matrix dosage form” may indicate that the dosage form comprises a prolonged release matrix as the sole
20 structure being responsible for prolonging the release. This, however, does not exclude that the dosage form may comprise an immediate release portion.

For some embodiments, the term “prolonged release coating dosage form” may indicate that the dosage form comprises a prolonged release coating as the sole
25 structure being responsible for prolonging the release. This, however, does not exclude that the dosage form may comprise an immediate release portion.

The release rates indicated always refer to the formulation such as a monolithic tablet or multi-particulates. The release rates will be chosen such that a pharmaceutical
30 composition can be administered e.g. on a twice a day or once a day basis, i.e. every

12 hours or every 24 hours. Typically, the release will occur by diffusion through the prolonged release matrix and/or coating, erosion of the prolonged matrix and/or coating or combinations thereof.

5 Release materials

The following description of suitable materials is to be understood as being not limiting. Rather, the release material may be any material that is known to be capable of imparting prolonged release properties on the active agents, hydromorphone and
10 naloxone, when being formulated into a dosage form.

Prolonged release matrix materials

The prolonged release material may be any material that is known to be capable of
15 imparting controlled release properties on the active agent when being formulated into a prolonged release matrix. Such materials may be hydrophilic and/or hydrophobic materials such as gums, cellulose ethers, acrylic polymers, protein-derived materials etc.

20 Prolonged materials may also include fatty acids, fatty alcohols, glyceryl esters of fatty acids, polyethylene glycols, mineral and oils and waxes. Fatty acids and fatty alcohols preferable are those with a C₁₀ to C₃₀ chain, preferably with a C₁₂ to C₂₄ chain and more preferably with a C₁₄ to C₂₀ chain or a C₁₆ to C₂₀ chain. Materials such as stearyl alcohol, cetostearyl alcohol, cetyl alcohol, myristyl alcohol and
25 polyalkylene glycols may be preferred. Waxes may be selected from natural and synthetic waxes such as beeswax, carnauba wax. Oils may be vegetable oils and include for example castor oil.

The prolonged release matrix materials which may be considered in the context of
30 the present invention may also be selected from cellulose ethers.

The term “cellulose ethers” comprises cellulose-derived polymers derivatized with at least alkyl and/or hydroxyalkyl groups which may be hydrophilic or hydrophobic.

- 5 For example, the prolonged release matrix material may be a hydrophilic hydroxy alkyl cellulose such as a hydroxy (C1 – C6) alkyl celluloses such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose and particularly preferably hydroxyethyl cellulose.
- 10 Examples of hydrophobic cellulose ethers include e.g. ethyl cellulose. The use of ethyl cellulose may be preferred. Hydrophobic cellulose ethers such as ethyl cellulose may be particularly suitable for imparting alcohol resistance to pharmaceutical compositions.
- 15 A particularly suitable material for prolonged release matrix formulations in accordance with the present invention may be selected from the group of acrylic resins. Such acrylic resins may be made from (meth)acrylic acid (co) polymers.

There are various types of (meth)acrylic acid (co)polymers available which may be
20 characterized according to the nature of their residues such as neutral (meth)acrylic acid (co)polymers, (meth)acrylic acid (co)polymers with anionic residues or (meth)acrylic acid ester copolymers with cationic residues.

Neutral (meth)acrylic acid (co)polymers include polymers having 95 to 100% by
25 weight of polymerized monomers having neutral residues. Monomers with neutral residues can be C₁-C₄ alkyl esters of acrylic or methacrylic acid such as methylmethacrylate, ethylmethacrylate, butylmethacrylate, methylacrylate, ethylacrylate and butylacrylate. For example, neutral (meth)acrylic acid (co)polymers may comprise 20 to 40 % by weight ethylacrylate and 60 to 80 % by
30 weight methylmethacrylate. Such polymers are e.g. available under the trade name

Eudragit[®] NE which is a copolymer of 30 % by weight ethylacrylate and 70 % by weight methylmethacrylate. This polymer is usually provided in the form of a 30 % or 40% aqueous dispersion (Eudragit[®] NE 30 D, Eudragit[®] NE 40 D or Eudragit[®] NM 30 D).

5

(Meth)acrylic acid (co)polymers with functional anionic residues may be (meth)acrylic acid (co)polymers having 25 to 95 % by weight of radically polymerised C₁ to C₄ alkyl esters of acrylic or methacrylic acid and 5 to 75 % by weight of methacrylate monomers with an anionic group in the alkyl residue. C₁ to C₄ alkyl esters of acrylic or methacrylic acid are again methylmethacrylate, ethyl methacrylate, butylmethacrylate, methylacrylate, ethylacrylate and butylacrylate. A (meth)acrylate monomer with an anionic group in the alkyl residue may be for example acrylic acid and preferably methacrylic acid. Such methacrylic acid copolymers with an anionic functional group may comprise e.g. 40 to 60 % by weight methacrylic acid and 60 to 40 % by weight methylmethacrylate or 60 to 40 % by weight ethyl acrylate. These types of polymers are available as Eudragit[®] L100 / Eudragit[®] L 12.5 or Eudragit[®] L 100-55 / Eudragit[®] L 30 D-55, respectively.

For example, Eudragit[®] L 100 is a copolymer of 50 % by weight methylmethacrylate and 50 % by weight methacrylic acid. It is also provided as a 12.5% solution (Eudragit[®] L 12.5). Eudragit[®] L 100-55 is a copolymer of 50 % by weight ethylacrylate and 50 % by weight methacrylic acid. It is also provided as 30 % dispersion (Eudragit[®] L 30 D-55).

(Meth)acrylic acid (co)polymers with an anionic functional group may also comprise 20 to 40 % by weight methacrylic acid and 80 to 60 % by weight methylmethacrylate. These types of polymers are usually available under the trade name Eudragit[®] S. It is also provided as a 12.5 % solution (Eudragit[®] S 12.5). Another type of methacrylic acid copolymers with an anionic functional group is available under the trade name Eudragit[®] FS which typically comprises 10 to 30 %

by weight methylmethacrylate, 50 to 70 % by weight methylacrylate and 5 to 15 % by weight methacrylic acid. Thus, Eudragit®FS may be a polymer of 25 % by weight methylmethacrylate, 65 % by weight methylacrylate and 10 % by weight methacrylic acid. It is usually provided as 30 % dispersion (Eudragit® FS 30 D).

5

(Meth)acrylic acid (co)polymers with functional cationic groups may be methacrylic acid copolymers with tertiary amino groups. Such polymers may comprise 30 % to 80 % by weight of radically polymerized C₁-C₄ alkyl esters of acrylic acid or methacrylic acid and 70 to 20 % by weight methacrylate monomers with a tertiary amino group in the alkyl rest.

10

Suitable monomers with a functional tertiary amino group are disclosed e.g. in US 4,705,695, column 3, line 64 to column 4, line 13. They include for example dimethylaminoethyl acrylate, 2-dimethylaminopropyl acrylate, dimethylaminopropyl methacrylate, dimethylaminobenzyl acrylate, dimethylaminobenzyl methacrylate, (3-dimethylamino-2,2-dimethyl)propyl acrylate, dimethylamino-2,2-dimethylpropylmethacrylate, (3-diethylamino-2,2-dimethyl)propyl acrylate and diethylamino-2,2-dimethylpropylmethacrylate. Particularly suitable is dimethylaminoethyl methacrylate. The amount of monomers with a tertiary amino group in the copolymer may vary between 20 to 70 %, between 40 to 60 %. The amount of C₁ to C₄ alkyl esters of acrylic or methacrylic acid may be within 70 to 30 % by weight. C₁ to C₄ alcohol esters of acrylic or methacrylic acid include methylmethacrylate, ethylmethacrylate, butylmethacrylate, methylacrylate, ethylacrylate and butylacrylate. A common (meth)acrylic acid (co)polymer with a tertiary amino group may comprise 20 to 30 % by weight methylmethacrylate, 20 to 30 % by weight butylmethacrylate and 60 to 40 % by weight dimethylaminoethyl methacrylate. For example the commercially available Eudragit® E 100 comprises 25 % by weight methylmethacrylate, 25 % by weight butylmethacrylate and 50 % by weight dimethylaminoethyl methacrylate. Another common commercially available

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polymer, Eudragit®E PO comprises copolymers of methylmethacrylate, butylmethacrylate and dimethylaminoethyl methacrylate in a ratio of 25:25:50.

Another type of (meth)acrylic acid (co)polymers with functional cationic groups is
5 (meth)acrylic acid (co)polymers with a quaternary amino group. This type of (meth)acrylic acid (co)polymers typically comprises 50 to 70 % of radically polymerized methylmethacrylate, 20 to 40 % by weight of ethylacrylate and 12 to 2 % by weight of 2-trimethylammoniummethyl methacrylate chloride. Such polymers are e.g. available under the trade names Eudragit®RS or Eudragit®RL.

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For example, Eudragit®RS comprises radically polymerised units of 65 % by weight methylmethacrylate, 30 % by weight ethylacrylate and 5 % by weight 2-trimethylammoniummethyl methacrylate chloride. Eudragit®RL comprises radically
15 polymerised units of 60 % by weight methylmethacrylate, 30 % by weight ethylacrylate and 10 % by weight 2-trimethylammoniummethyl methacrylate chloride.

Prolonged release matrix materials which are particularly suitable for the present invention are e.g. the neutral (meth)acrylic acid (co)polymers or the (meth)acrylic acid (co)polymers with anionic functional groups. One may for example use
20 mixtures of these types of polymers. For example, one may use Eudragit®NE as a neutral (meth)acrylic acid (co)polymer and Eudragit®RSPO as a (meth)acrylic acid (co)polymer with an anionic functional group. One may also use a mixture of these types of polymers.

25 However, one may also use a mixture of (meth)acrylic acid (co)polymers and other prolonged release matrix materials such as cellulose ethers. For example, one may use a mixture of a neutral (meth)acrylic acid (co)polymer and a hydrophobic cellulose ether. A particularly suitable example is the combination of a Eudragit®NE together with ethyl cellulose. Another prolonged release material which may be used
30 for the present invention may be polymers such as polyethylene oxide.

As regards polyethylene oxides, particularly those polyethylene oxides with a molecular weight in the range of 1×10^5 - 5×10^5 may be used.

5 Prolonged release materials which are particularly suitable for the present invention are e.g. the neutral (meth)acrylic acid (co)polymers or the (meth)acrylic acid (co)polymers with anionic functional groups. One may for example use mixtures of these types of polymers.

10 For example, one may use Eudragit®NE as a neutral (meth)acrylic acid (co)polymer and Eudragit®RSPO as a (meth)acrylic acid (co)polymer with an anionic functional group. One may also use a mixture of these types of polymers. The use of (meth)acrylic acid (co)polymers can be particularly suitable for increasing hardness/breaking strength upon heat treatment .

15

However, one may also use a mixture of (meth)acrylic acid (co)polymers and other prolonged release matrix materials such as cellulose ethers. For example, one may use a mixture of a neutral (meth)acrylic acid (co)polymer and a hydrophobic cellulose ether. A particularly suitable example is the combination of a

20 Eudragit®NE together with ethyl cellulose. Another example is a mixture of cellulose ether such as hydrophobic cellulose ethers (e.g. ethyl cellulose) with a fatty alcohol (e.g. stearyl alcohol). A mixture of (meth)acrylic acid (co)polymers such as neutral (meth)acrylic acid (co)polymer (e.g. Eudragit®NE) and cellulose ethers such as hydrophobic cellulose ethers (e.g. ethyl cellulose) may also comprise a fatty
25 alcohol (such as stearyl or cetostearyl alcohol) as a further prolonged release matrix material.

The amount of prolonged release material(s) in the prolonged release formulation may be of about 5 to 90 % by weight, of about 10 to 70% by weight, of about 20 to
30 60 % by weight, of about 20% to about 55% by weight, of about 25% to about 50%

by weight, of about 25% to about 45% by weight and preferably of about 30 to about 40% by weight based on the weight of the pharmaceutical composition. The amount of prolonged release material that is incorporated into the composition can be one way of adjusting the prolonged release properties. For example, if the amount of

5 prolonged release material is increased, the release can be further prolonged. The aforementioned amounts refer to the overall content of prolonged release materials in a pharmaceutical composition. These amounts may thus refer to a mixture of various prolonged release materials such as a neutral (meth)acrylic acid (co)polymer, a hydrophobic cellulose ether and/or a fatty alcohol.

10

If cellulose ether is among the prolonged release materials, it will typically be present in an amount of about 5% to about 50% by weight, of about 5% to about 45% by weight, of about 5% to about 40% by weight, of about 5% to about 35% by weight, of about 5% to about 30% by weight, of about 5% to about 25% by weight,

15 of about 5% to about 20% by weight such as of about 5% by weight, of about 7% by weight, of about 10% by weight, of about 15% by weight, of about 18% by weight or of about 20% by weight based on the weight of the pharmaceutical composition.

20

If fatty alcohol is among the prolonged release materials, it will typically be present in an amount of about 5% to about 50% by weight, of about 5% to about 45% by weight, of about 5% to about 40% by weight, of about 5% to about 35% by weight, of about 10% to about 30% by weight, of about 10% to about 25% by weight such as of about 10% by weight, of about 15% by weight, of about 20% by weight or about 25% by weight based on the weight of the pharmaceutical composition.

25

If (meth)acrylic acid (co)polymer is among the prolonged release materials, it will typically be present in an amount of about 5% to about 50% by weight, of about 5% to about 45% by weight, of about 5% to about 40% by weight, of about 5% to about 35% by weight, of about 10% to about 30% by weight, of about 10% to about 25%

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by weight such as of about 10% by weight, of about 15% by weight, of about 20% by

weight or about 25% by weight based on the weight of the pharmaceutical composition.

5 The person skilled in the art is further aware that such a prolonged release matrix may also contain other pharmaceutically acceptable ingredients and excipients which are conventional in the pharmaceutical art such as lubricants, fillers, binders, flowing agents, colorants, flavorings, surfactants, pH-adjusters, anti-tacking agents and granulating aids. These excipients will typically have no substantial impact on the overall release behavior of the pharmaceutical dosage form.

10

Typical examples of fillers (diluent) comprise lactose, preferably anhydrous lactose, glucose, saccharose, starch and their hydrolysates, microcrystalline cellulose, cellatose, sugar alcohols such as sorbitol or mannitol, calcium salts like calcium hydrogen phosphate, dicalcium- or tricalcium phosphate. Granulating aids comprise 15 *inter alia* povidone. Flowing agents and lubricants comprise *inter alia* highly dispersed silica, talcum, magnesium oxide, calcium stearate, magnesium stearate, sodium stearyl fumarate, fast like hydrated castor oil and glyceryl dibehenate. Binders can include hydroxypropylmethyl cellulose (hypromellose), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose, polyvinyl pyrrolidone (povidone), acetic 20 acid vinyl ester (copovidone) and carboxymethylcellulose sodium. Anti-tacking agents may include glycerol monostearate. Furthermore, a matrix-based dosage form may e.g. comprise a cosmetic coating.

Prolonged release coating materials

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As mentioned above, prolonged release characteristics of a pharmaceutical dosage form may also be achieved by a film coating that governs the release of the active agents from the dosage form. To this end, the pharmaceutical dosage form may comprise a carrier, which is associated with the hydromorphone and naloxone. For

example, one may use nonpareil beads, sugar beads etc. on and/or into which the pharmaceutically active agents are disposed.

Such active-associated carriers may then be overcoated with a coating that provides
5 prolonged release characteristics. Particularly suitable prolonged release coating materials include hydrophobic polymers such as cellulose ethers and/or acrylic polymer resins. Ethylcellulose may be preferred. However, prolonged release coatings may be made from materials which are common in the art.

10 They may thus be selected from e.g. prolonged release materials selected e.g. from (i) an alkylcellulose; (ii) an acrylic polymer; (iii) polyvinylalcohol or (iv) mixtures thereof. Hydrophobic representatives of the afore-mentioned groups can be preferred. The coating may be applied in the form of an organic or aqueous solution or dispersion.

15 In some embodiments, the controlled release coating is derived from an aqueous dispersion of the hydrophobic controlled release material. The coated composition can then be cured. In preferred embodiments, the controlled release coatings include a plasticizer such as those described herein below.

20 In certain embodiments, one may coat with an amount of coating material which is sufficient to obtain a weight gain level from about 2 to about 20%, e.g., about 2 to about 15% and preferably about 5 to about 10% such as 6%, 7%, 8% or 9% in order to obtain sufficiently prolong the release from the formulation..

25 Cellulosic materials and polymers, including alkyl celluloses are prolonged release materials well suited for coating substrates, e.g., beads, granules, tablets, etc. according to the invention. Simply by way of example, one preferred alkyl cellulosic polymer is ethyl cellulose. One commercially available aqueous dispersion of ethyl
30 cellulose is Aquacoat® such as Aquacoat® ECD30 (FMC Corp., Philadelphia,

Pennsylvania, U.S.A.). Aquacoat is prepared by dissolving the ethyl cellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudo latex.

- 5 Another aqueous dispersion of ethyl cellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pennsylvania, U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline
10 solution to obtain an aqueous dispersion which can be applied directly onto substrates.

- In other of the present invention, the prolonged release coating material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid
15 and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride) and glycidyl
20 methacrylate copolymers.

- In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonium methacrylate copolymers. Ammonium methacrylate copolymers are well known in the art, and are described as fully polymerized copolymers of acrylic and
25 methacrylic acid esters with a low content of quaternary ammonium groups. Typical examples include Eudragit® RS30D which is a low permeability ammonium methacrylate polymer and Eudragit®RL30D which is a high permeability ammonium methacrylate polymer. Eudragit RL and Eudragit RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however,
30 dosage forms coated with Eudragit RL and RS are pH-independent.

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The acrylic coatings may comprise a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Trade names Eudragit®RL30D and Eudragit®RS30D, respectively. The Eudragit®RL/RS
5 dispersions of the present invention may be mixed together in any desired ration in order to ultimately obtain a prolonged-release formulation having a desirable dissolution profile.

Other polymers which can be used as a prolonged release coating materials if they
10 are applied at sufficient amounts are e.g. hydrophilic polymers such as hyrdoxypropylmethylcellulose.

The above mentioned coatings may also be applied in combination. Further it is possible to influence the release properties of a dosage form by increasing the
15 amount of the coating material and thus the thickness of the coating.

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic controlled release material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material may
20 further improve the physical properties of the prolonged release coating. For example, because ethyl cellulose has a relatively high glass transition temperature and may not form flexible films under normal coating conditions, it can be preferred to incorporate a plasticizer into an ethyl cellulose coating containing prolonged release coating before using the same as a coating material. Generally, the amount of
25 plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 % by weight of the film-former.

Examples of suitable plasticizers for ethyl cellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate,
30 and triacetin, although it is possible that other water-insoluble plasticizers (such as

acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

- 5 Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit®RL/RS lacquer solutions include
- 10 polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin.

- It should be noted that the prolonged release coatings may comprise other components such as hydrophilic substances including hydrophilic polymers such hydroxypropylmethylcellulose (HPMC), polyethyleneglycols etc. These components
- 15 may be used to adjust the prolonged release characteristics of the coatings. In case of e.g. HPMC, the substances may act as pore formers. The coating may, of course, also comprise additional pharmaceutically acceptable excipients, e.g. as set out above for the matrices.

20 Immediate release materials

- Typical pharmaceutically acceptable excipients used in immediate release dosage forms are disintegrants, diluents, lubricants, glidants, anti-tacking agents, plasticizers, colorants, flavorants, binders, pH adjusters and the like. These excipients
- 25 (with the exception of disintegrants) are to be chosen such that they do not substantially alter the immediate release *in vitro* release rates.

- It can be preferred for the pharmaceutical compositions of the present invention to comprise at least a diluent and optionally a disintegrant as pharmaceutically
- 30 acceptable excipients, particularly if the pharmaceutical compositions of the present

- 50 -

invention are provided as a tablet. It can also be preferred for the pharmaceutical compositions of the present invention to comprise at least a disintegrant and optionally a diluent as pharmaceutically acceptable excipients, particularly if the pharmaceutical compositions of the present invention are provided as a tablet.

- 5 It can further be preferred to use excipients which act both as a disintegrant and a diluent.

The disintegrant, for example, will ensure that the tablet after administration will rapidly disintegrate so that the active agents become readily available for absorption.

10

Diluents may be selected from but are not limited to lactose such as lactose monohydrate, lactose anhydrous, starch such as maize starch, pregelatinized starch, microcrystalline cellulose, glucose, Mannitol, Maltitol, StarLac® (85% spray dried lactose, 15% maize starch), saccharose, calcium salts like calcium hydrogen
15 phosphate or any combinations of the above.

Disintegrants may be selected from but are not limited to *inter alia* StarLac® (85% spray dried lactose, 15% maize starch), croscarmellose such as croscarmellose sodium, sodium starch glycolate, crospovidone, alginic acid, or low substituted
20 hydroxypropyl cellulose.

A combination of lactose and starch such as the Starlac® product can be particularly preferred as it combines the properties of a filler and a disintegrant.

- 25 Glidants and lubricants may be selected but are not limited to *inter alia* highly dispersed silica, talcum, magnesium oxide, magnesium stearate, sodium stearyl fumarate etc.

Flowing agents and lubricants comprise *inter alia* highly dispersed silica, talcum,
30 magnesium oxide, magnesium stearate, sodium stearyl fumarate etc.

If pharmaceutical compositions of the present invention are provided as a tablet, they may be coated for identification purposes with a cosmetic coating. Such coatings will have no substantial impact on the immediate release properties of the pharmaceutical compositions in accordance with the invention.

Preferably, one can use a combination of e.g. starch and lactose as disintegrant. Lactose alone may at the same time function as a filler. A particularly preferred embodiment relies on the product Starlac®, a combination of lactose 85% and starch 15%, which may function both as a disintegrant and as a filler. The combined filler/disintegrant may be comprised within the pharmaceutical composition in an amount of about 40% to about 90%, preferably in an amount of about 50% to about 85% and even more preferably in an amount of about 60% to about 80% by weight based on the weight of the composition. These numbers particularly apply if an excipient having a dual function both as a disintegrant and a filler such as Starlac® is used.

Preferred embodiments of the present invention relate to:

1. Oral pharmaceutical dosage form comprising hydromorphone 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.

2. Dosage form for use according to 1, 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, Crohn's disease, 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.

10

3. Dosage form for use according to 1 or 2, 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.

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4. Dosage form for use according to any one of 1 to 3, 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

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1 and 2 diabetes, intestinal infections and intestinal mycosis, 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.

5 5. Dosage form for use according to any one of 1 to 4, 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, previous ileo-
10 caecal resection, post-radiation enteropathy, autonomic neuropathy including autonomic neuropathy in type 1 and 2 diabetes, intestinal infections and intestinal mycosis, 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.

15 6. Dosage form for use according to any one of 1 to 5, 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 and hyperactivity of the immune system, and/or
20 wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, burn injury, trauma and cholecystitis.

 7. Dosage form for use according to 1, wherein said at least one further
25 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
30 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.

8. Dosage form for use according to 1 or 7, wherein said at least one
5 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-
10 radiation enteropathy, autonomic neuropathy including autonomic neuropathy in type 1 and 2 diabetes, intestinal infections and intestinal mycosis.

9. Dosage form for use according to any one of 1, 7 or 8, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria,
15 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, previous ileo-caecal resection, post-radiation enteropathy, autonomic neuropathy including autonomic neuropathy in type 1 and 2 diabetes, intestinal infections and intestinal
20 mycosis.

10. Dosage form for use according to any one of 1, 7, 8 or 9, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth syndrome,
25 small intestinal pseudo-obstruction, surgical blind loop, small intestinal obstruction, scleroderma, food intolerance and hyperactivity of the immune system.

11. Dosage form for use according to 1, wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis,
30 cholangitis, burn injury, trauma and cholecystitis.

12. Dosage form for use according to 1 or 11, wherein said at least one further disease iii) is selected from the group consisting of cholangitis, burn injury and cholecystitis.

5 13. Dosage form for use according to 1, 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
10 colitis, diverticulitis, fistulae, Crohn's disease, previous ileo-caecal resection, post-radiation enteropathy, intestinal infections, intestinal mycosis, obesity, autism, metabolic syndrome, rheumatoid arthritis, allergy, and sepsis, and/or wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, trauma and cholecystitis.

15

14. Dosage form for use according to 1 or 13, 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,
20 scleroderma, food intolerance, hyperactivity of the immune system, colorectal cancer, ulcerative colitis, diverticulitis, fistulae, previous ileo-caecal resection, post-radiation enteropathy, intestinal infections, intestinal mycosis, obesity, autism, metabolic syndrome, rheumatoid arthritis, allergy, and sepsis, and/or wherein said at least one further disease iii) is selected from the group consisting of appendicitis,
25 pancreatitis, cholangitis, trauma and cholecystitis.

15. Dosage form for use according to any one of 1, 13 or 14, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth syndrome,
30 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, intestinal infections and intestinal mycosis, and/or wherein said at least one further disease iii) is selected from the group consisting of
5 appendicitis, pancreatitis, cholangitis, trauma and cholecystitis.

16. Dosage form for use according to any one of 1, 13, 14 or 15, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth
10 syndrome, small intestinal pseudo-obstruction, surgical blind loop, small intestinal obstruction, scleroderma, food intolerance, hyperactivity of the immune system, previous ileo-caecal resection, post-radiation enteropathy, intestinal infections and intestinal mycosis, and/or wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, trauma and
15 cholecystitis.

17. Dosage form for use according to any one of 1, 13, 14, 15 or 16, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth
20 syndrome, small intestinal pseudo-obstruction, surgical blind loop, small intestinal obstruction, scleroderma, food intolerance and hyperactivity of the immune system, and/or wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, trauma and cholecystitis.

25 18. Dosage form for use according to 1, 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
30 colitis, diverticulitis, fistulae, previous ileo-caecal resection, post-radiation

enteropathy, intestinal infections, intestinal mycosis, obesity, autism, metabolic syndrome, rheumatoid arthritis, allergy and sepsis.

19. Dosage form for use according to 1 or 18, wherein said at least one
5 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-
10 radiation enteropathy, intestinal infections and intestinal mycosis.

20. Dosage form for use according to any one of 1, 18 or 19, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth syndrome,
15 small intestinal pseudo-obstruction, surgical blind loop, small intestinal obstruction, scleroderma, food intolerance, hyperactivity of the immune system, previous ileo-caecal resection, post-radiation enteropathy, intestinal infections and intestinal mycosis.

20 21. Dosage form for use according to any one of 1, 18, 19 or 20, 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 and hyperactivity of the immune system.

25 22. Dosage form for use according to 1, wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, trauma and cholecystitis.

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23. Dosage form for use according to 1 or 22, wherein said at least one further disease iii) is selected from the group consisting of cholangitis and cholecystitis.

5 24. Dosage form for use according to any one of 1 to 23, wherein i) pain is not a symptom of the at least one further disease ii) or the at least one further disease iii).

10 25. Dosage form for use according to any one of 1 to 24, wherein said intestinal dysbiosis and/or said increased risk for intestinal bacterial translocation is not induced by an opioid agonist but by said at least one further disease ii) or iii).

26. Dosage form for use according to any one of 1 to 25, wherein said pain is moderate to severe pain.

15 27. Dosage form for use according to any one of 1 to 26, wherein hydromorphone 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.

20 28. Dosage form for use according to any one of 1 to 27, wherein the pain treatment regimen excludes the co-administration of an active agent directed to the improvement of the intestinal dysbiosis and/or of an active agent decreasing the risk for intestinal bacterial translocation and/or of an active agent directed to the
25 improvement of opioid-induced constipation and/or opioid-induced bowel dysfunction.

29. Dosage form for use according to any one of 1 to 28, wherein the dosage form comprises hydromorphone or a pharmaceutically acceptable salt thereof
30 in an amount range of equivalent to about 1 mg to about 64 mg hydromorphone HCl

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and naloxone or a pharmaceutically acceptable salt thereof in an amount range of equivalent to about 1 mg to about 256 mg naloxone HCl.

30. Dosage form for use according to any one of 1 to 29, wherein the
5 dosage form comprises hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio range corresponding to about 2:1 to about 1:3 of hydromorphone HCl:naloxone HCl.

31. Dosage form for use according to 30, wherein the dosage form
10 comprises hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio range corresponding to about 2:1 to about 1:2 of hydromorphone HCl:naloxone HCl.

32. Dosage form for use according to 31, wherein the dosage form
15 comprises hydromorphone or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio corresponding to about 1:2 of hydromorphone HCl:naloxone HCl.

33. Dosage form for use according to any one of 1 to 32, wherein the
20 dosage form is a prolonged release dosage form.

34. Dosage form for use according to 33, wherein the dosage form comprises a prolonged release matrix.

25 35. Dosage form for use according to 34, wherein the prolonged release matrix comprises a prolonged release material selected from the group consisting of hydrophobic or hydrophilic polymers, protein-derived material, gums, substituted or unsubstituted hydrocarbons, digestible carbohydrates, fatty acids, fatty alcohols, glyceryl esters of fatty acids, natural and synthetic oils and natural and synthetic
30 waxes.

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36. Dosage form for use according to 33, wherein the dosage form comprises a prolonged release coating.

37. Dosage form for use according to any one of 1 to 32, wherein the
5 dosage form is an immediate release dosage form.

38. Dosage form for use according to any one of 1 to 37, wherein the dosage form is a dosage form selected from the group consisting of a tablet, a capsule, a multi-particulate, a dragée, a granulate and a powder.
10

EXAMPLES

Example 1: Influence of codeine on the gastrointestinal (GI) microbiota, the GI metagenome (i.e. the whole genetic information of the microbial community) and the
15 host metabolome (i.e. products and/or metabolites produced by the microbial community).

The main goal of this example resides in the determination of upper and mid GI activity and structural integrity and several GI microbiota parameters including
20 metabolomic parameters of plasma (as a result of bacterial metabolism in the upper/mid GI tract) in healthy subjects comparing the situation prior to and after opioid administration (see also Figure 1).

Ten healthy volunteers will be recruited and a codeine-dose of 120 mg/d (30 mg four
25 times daily) will be given for ten days. Diet will not be restricted and the bowel/stool behavior will be noted daily by the volunteers. Before the first dose and after the last dose, individuals will undergo upper- and lower-GI tract endoscopy and luminal contents and mucosal biopsies will be taken. Luminal contents will additionally be preserved with glycerol for subsequent transplantation into gnotobiotic mice (see
30 Example 2). Plasma and urine samples will be collected. Volunteers will also

undergo a H₂ breath test with oral lactulose to assess microbial metabolic activity (especially methane production) and orocecal transit time. Since bowel preparation for lower GI endoscopy influences the results of H₂ breath tests, only a sigmoidoscopy without previous oral lavage will be performed for these experiments.

5

All of the following objectives are based on the comparison between day 0 and day 10 (see also Figure 1).

Objective 1: Comparison of the small-bowel microbiota based on comparative 16S rDNA-based microbial community profiling.

10

Objective 2: Comparative metagenome and metatranscriptome (i.e. the transcriptome of the microbiota) analyses of individual samples (luminal contents only).

Objective 3: Comparative metabolome analyses by assessing the plasma and urine-samples for metabolome signatures based on MS-techniques. The comparison of the metabolome spectra will reveal altered metabolite profiles, which may then be correlated to changes in the individual metagenomes/metatranscriptomes to identify the molecular basis of microbiota caused changes in metabolism.

20

Objective 4: Assessing the epithelial barrier function of mucosal biopsies and performing a mucosal immune-phenotyping based on IHC and FACS; assessing of selected targets of barrier function (such as e.g. claudins) and the mucosal immune system (pro- vs. anti-inflammatory) based on qRT-PCR.

25

Objective 5: Transplantation of microbiota into gnotobiotic mice and analysis of gut motility, mucosal barrier function and the mucosal immune-system on the basis of this animal-model.

Example 2: Effects on intestinal microflora composition and bacterial translocation following single or multiple oral doses of hydromorphone and a combination of hydromorphone and naloxone in mice.

- 5 The main goal of this example resides in the determination of several GI microbiota parameters and GI structural parameters including impact on local and systemic immune response / inflammation in an animal model comparing the effects of hydromorphone (C) and hydromorphone/naloxone (D) on said parameters to baseline (A) and placebo (B). Indications in brackets refer to the groups shown in Figure 2.

10

The objective is to demonstrate differences for the intestinal microflora composition and bacterial translocation between hydromorphone and hydromorphone/naloxone. To this aim, specified serum, gastrointestinal tract samples and mesenteric lymph nodes are collected according to the protocol as outlined in the following. Further,
15 the intestinal integrity is analyzed using marker molecules such as FITC-dextran (permeability assay that is carried out in living animals), and the samples of the gastrointestinal tissue are histologically analyzed. Also, the intestinal motility is analyzed by using the charcoal test as outlined below.

- 20 Male mice at an approximal age of 5 to 10 weeks are used in the study. 6 to 8 animals are used per group in groups A) to D) as shown in Figure 2.

- Appropriate amounts of hydromorphone and naloxone are dissolved in sterile water to make formulations containing the following range of nominal concentrations of the actives (see also Figure 2). For hydromorphone: 3 to 9 mg/ml hydromorphone (see also group C in Figure 2); and for hydromorphone and naloxone [with a ratio of
25 of hydromorphone to naloxone of 1:2]: 3 to 9 mg/ml hydromorphone + 6 to 18 mg/ml naloxone (see also group D in Figure 2). It is intended to select one or several appropriate concentrations to be tested in the animals for tissue sampling by initially conducting the charcoal test-study in a first setup of animals (see below).

Dosing Procedures:

Animals are administered the dose by oral gavage either once (single administration) or twice (bid) / three times (tid) a day and then for 7 days and once on the 8th day.

- Alternatively, in case of dosing over several days, the dosing may not last for the full 8 days but may be shorter. Prior to the first dose administration of the day, the dose formulation vials designated for that day are removed from the refrigerator, briefly mixed, and allowed to come to room temperature, where the vials remain throughout the day. After the last dose on day 8 (or earlier, see above), all animals fasten through euthanasia. The dose volume is based on the animal's body weight on Day 1. This protocol is generally also followed for a single dose administration.

Observation of Animals:

Antemortem Observations

- During the post-dose, in-life portion of the study, observation of animals for general health and mortality is performed twice daily (AM and PM) on weekdays and once daily on weekends. During the acclimation period, animals are observed once daily. Only healthy animals are dosed. As noted above, permeability assays with FITC-dextran according to a standard protocol are carried out in dosed animals in the in-life portion of the study.

Body Weights

- Individual body weights are recorded prior to administration of the first dose on Day 1. The body weight determinations prior to Day 1 dose administration is used to determine the dose administered for all subsequent doses. Subsequent body weights are recorded daily after the 2nd dose of the day on Days 2 through 7.

Sample Collection:

It is intended to carry out the sample collection from two different experimental setups: i) groups of animals as outlined in Figure 2, in which the charcoal test as outlined below is carried out; and ii) groups of animals as outlined in Figure 2, in which the samples as outlined below are collected. It is intended to carry out setup i) prior to setup ii); as noted above, this may result in the selection of one or several appropriate concentrations of the actives to be used in setup ii).

Charcoal Test of Intestinal Motility

Fifteen minutes after a single dosing or after the last dosing (in the case of multiple administrations), 0.1 ml of charcoal suspension (5% activated charcoal powder, 10% gum Arabic in water) is delivered to the stomach of each mouse using a gavage needle.

Thirty minutes after charcoal delivery, animals are euthanized. The abdominal cavity of each mouse is opened and the edge of the charcoal meal is tied off. The entire small intestine (from the stomach at the pylorus to the caecum) is removed. Its full length and the length of charcoal meal traveled is measured in centimeters. Intestinal transit is expressed as the percentage of intestine length containing the meal, i.e. $100 \times (\text{pylorus to meal front} / \text{pylorus to caecum length})$. Following measurements, the small intestine is discarded, along with the carcass.

Serum; mesenteric lymph nodes; gastrointestinal tract luminal content and mucosal scrapings

In order to minimize contamination during sample collection, the following measures are invoked:

- Sterile tubes (purchased pre-sterilized or autoclaved in-house) are used for all samples.

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- Samples are collected as soon after euthanasia as possible.
- Sterile instruments are used to handle all samples. Instruments are disinfected and/or heat sterilized between each separate sample collection.
- All personnel collecting samples wear disposable gloves, as well as
5 sterilized disposable labcoats, shoe covers, masks, and bonnets. Gloves are sprayed with 70% isopropyl alcohol prior to sample collection.

Serum

An hour after single dosing or after the last dosing (multiple administrations), each
10 animal is anesthetized and blood (maximum obtainable volume) is collected by cardiac puncture into a syringe. Blood is transferred into centrifuge tubes and allowed to clot at room temperature for a minimum of 5 minutes, after which the blood is centrifuged for 10 min at 10,000 rpm at room temperature. Serum is collected and placed on dry ice prior to storage in a -80°C freezer. Following blood
15 collection, animals are euthanized.

Mesenteric lymph nodes (MLNs)

Following euthanasia, the abdomen is opened. The mesenteric root is presented and the mesenteric net unfolded. The mesenteric lymph nodes (MLNs) are removed and surrounding fat is removed. The MLNs are then weighed into sterilized tubes.
20 Following weighing, the MLNs are frozen in liquid nitrogen. Following freezing, the MLNs are placed on dry ice prior to storage in a -70°C freezer (lymph nodes at -20°C).

Stomach and Intestine

Following removal of the mesenteric lymph nodes, the gastrointestinal tract (from
25 the stomach through the colon) is removed. The intestine is uncoiled with removal of mesenteric adhesions. The gastrointestinal tract is divided into the following sections: stomach; small intestine; caecum; colon. The stomach is discarded. The

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small intestine is spread in a meandering pattern and the colon is spread to its length. The small intestine and colon are placed alongside a ruler or similar reference, and photographed separately. The lengths of the small intestine and colon are recorded.

Luminal Contents (small intestine, caecum, colon)

- 5 The small intestine, caecum, and colon are cut longitudinally. The contents of each is individually collected into separate containers with a small spatula or similar instrument, taking care to cause as little injury to the tissue as possible. The weight of the contents collected from each portion is recorded. The weights of the small intestine, caecum, and colon following removal of the contents are also recorded.
- 10 Collected luminal contents samples are then frozen in liquid nitrogen. Luminal contents samples are then placed on dry ice before transfer to a -80°C freezer.

Mucosal Scraping (small intestine, caecum, colon)

- A buffer solution for collection, storage, and shipment of collected mucosal scraping samples is prepared: RLT buffer (Qiagen; catalog number 79216) is fortified with
- 15 1% beta-Mercaptoethanol (Applichem; catalog number A1108) and thoroughly mixed, then filter sterilized into a sterile RNase free Eppendorf cup, yielding sterile mucosal scraping buffer solution.

Following removal of the luminal contents from the small intestine, caecum, and colon, the small intestine is divided into the duodenum, jejunum, and ileum.

- 20 Residual luminal content is removed from the duodenum, jejunum, ileum, caecum, and colon by swaying in phosphate buffered saline (PBS) 10% fetal calf serum (FCS) at approximately 37°C. Following removal of residual luminal contents, an approximately 2 cm length of the mucosa is separated from the remaining tissue by sweeping or scraping along the luminal tissue from proximal to distal using a long
- 25 thin metal spatula or similar instrument. These mucosal scrapings are collected separately by organ (duodenum, jejunum, ileum, caecum, colon) and weighed into individual sterilized Eppendorf CUBE safelock snap-cap tubes or similar containing

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350 µL of the prepared sterile mucosal scraping buffer solution. The tubes are closed, vortexed, and the samples frozen in liquid nitrogen. Samples are then placed on dry ice before transfer to a -80°C freezer. Remaining gastrointestinal tissue is preserved for immuno- and histochemical analysis of epithelial barrier, mucin
5 expression, tight junctions (e.g. ZO-1, claudin proteins, actin) and Paneth cells (e.g. extent of granulas, analysis of defensin immunoreactivity) according to standard protocols.

Read out: The body weight and the food intake are assessed daily; for the baseline group and the study end, the following parameters are determined: length and weight
10 of intestine / intestinal microbiota composition by 16SrDNA (small intestine and caecum) / microbial count in mesenteric lymph nodes (translocation) / concentration of LPS, sCD14, LBP, TNF- α (heart blood) / IL-6, TNF α mRNA expression in mucosal scrapings (small intestine, colon, caecum) / metabolome analysis / intestinal permeability and intestinal histology.

15

CLAIMS

1. Oral pharmaceutical dosage form comprising hydromorphone 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.
2. Dosage form for use according to claim 1, wherein said at least one further disease ii) is 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, 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, and/or wherein said at least one further disease iii) is selected from the group consisting of cirrhosis, hepatitis, appendicitis, pancreatitis, chronic kidney disease and cholecystitis.
3. Dosage form for use according to claim 1, wherein said at least one further disease ii) is 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,

- sepsis, 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,
- 5 vaginal mycosis, intestinal mycosis, multiple system atrophy, food intolerance, intestinal infections, gallstones and hyperactivity of the immune system, and/or wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis and cholecystitis.
- 10 4. Dosage form for use according to claim 1, 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
- 15 cancer, ulcerative colitis, diverticulitis, fistulae, Crohn's disease, 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
- 20 iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, burn injury, trauma and cholecystitis.
5. Dosage form for use according to claim 1 or 4, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria,
- 25 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
- 30 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.

5

6. Dosage form for use according to any one of claims 1, 4 or 5, 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
10 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 and intestinal mycosis, and/or wherein said at least one further disease iii) is selected from the group
15 consisting of appendicitis, pancreatitis, cholangitis, burn injury, trauma and cholecystitis.

7. Dosage form for use according to any one of claims 1, 4, 5 or 6, wherein said at least one further disease ii) is selected from the group consisting of
20 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, previous ileo-caecal resection, post-radiation enteropathy, autonomic neuropathy including autonomic neuropathy in type 1 and 2 diabetes, intestinal infections and
25 intestinal mycosis, 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.

8. Dosage form for use according to any one of claims 1, 4, 5, 6 or 7,
30 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 and hyperactivity of the immune system, and/or wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, burn injury, trauma and
5 cholecystitis.

9. Dosage form for use according to claim 1, 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
10 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
15 syndrome, rheumatoid arthritis, allergy, diabetes mellitus including type 2 diabetes and sepsis.

10. Dosage form for use according to claim 1 or 9, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria,
20 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
25 1 and 2 diabetes, intestinal infections and intestinal mycosis.

11. Dosage form for use according to any one of claims 1, 9 or 10, wherein said at least one further disease ii) is selected from the group consisting of achlorhydria, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth
30 syndrome, small intestinal pseudo-obstruction, surgical blind loop, small intestinal obstruction, scleroderma, food intolerance, hyperactivity of the immune system,

previous ileo-caecal resection, post-radiation enteropathy, autonomic neuropathy including autonomic neuropathy in type 1 and 2 diabetes, intestinal infections and intestinal mycosis.

5 12. Dosage form for use according to any one of claims 1, 9, 10 or 11, 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 and hyperactivity of the immune system.

10

 13. Dosage form for use according to claim 1, wherein said at least one further disease iii) is selected from the group consisting of appendicitis, pancreatitis, cholangitis, burn injury, trauma and cholecystitis.

15

 14. Dosage form for use according to claim 1 or 13, wherein said at least one further disease iii) is selected from the group consisting of cholangitis, burn injury and cholecystitis.

 15. Dosage form for use according to any one of claims 1 to 14, wherein
20 i) pain is not a symptom of the at least one further disease ii) or the at least one further disease iii).

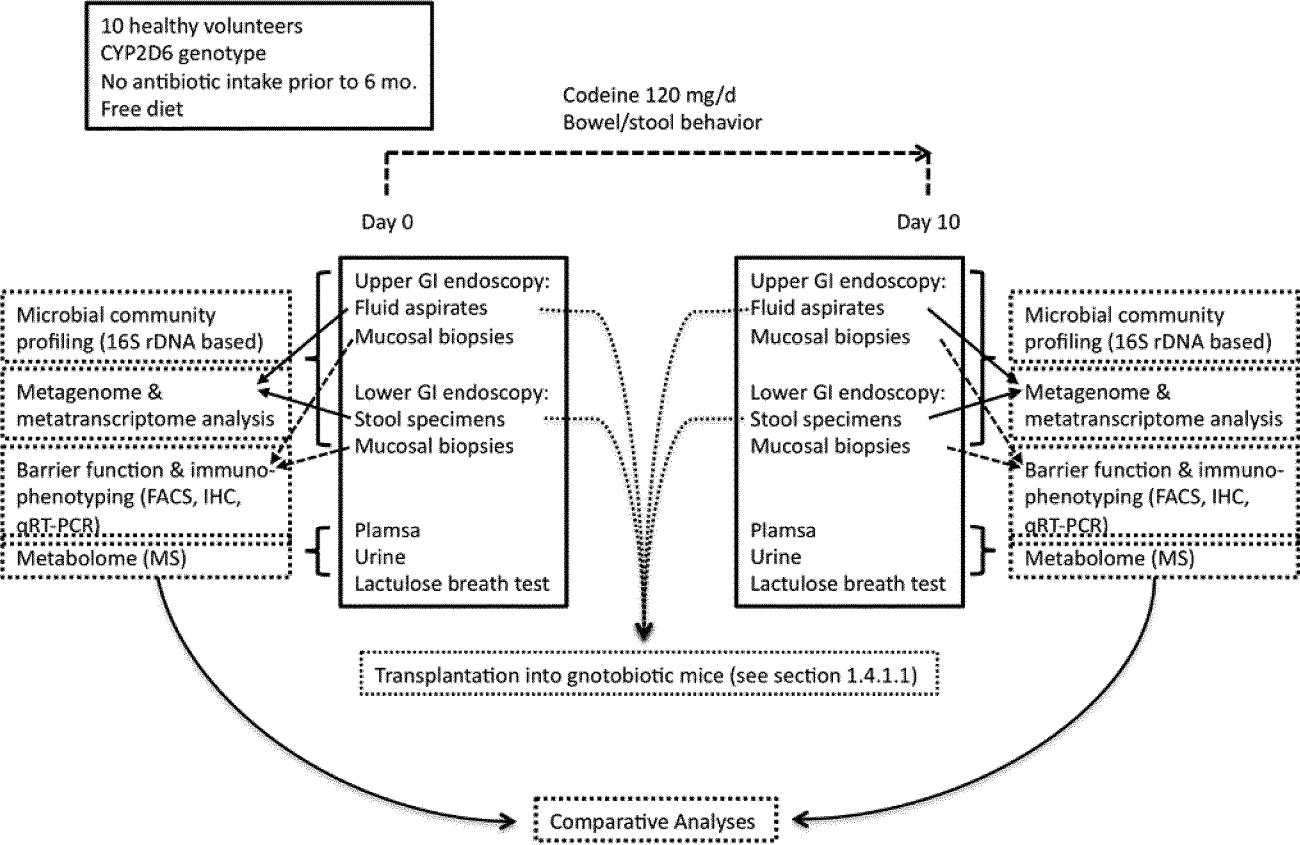
 16. Dosage form for use according to any one of the preceding claims, wherein said intestinal dysbiosis and/or said increased risk for intestinal bacterial
25 translocation is not induced by an opioid agonist but by said at least one further disease ii) or iii).

 17. Dosage form for use according to any one of the preceding claims, wherein the pain treatment regimen excludes the co-administration of an active agent
30 directed to the improvement of the intestinal dysbiosis and/or of an active agent decreasing the risk for intestinal bacterial translocation and/or of an active agent

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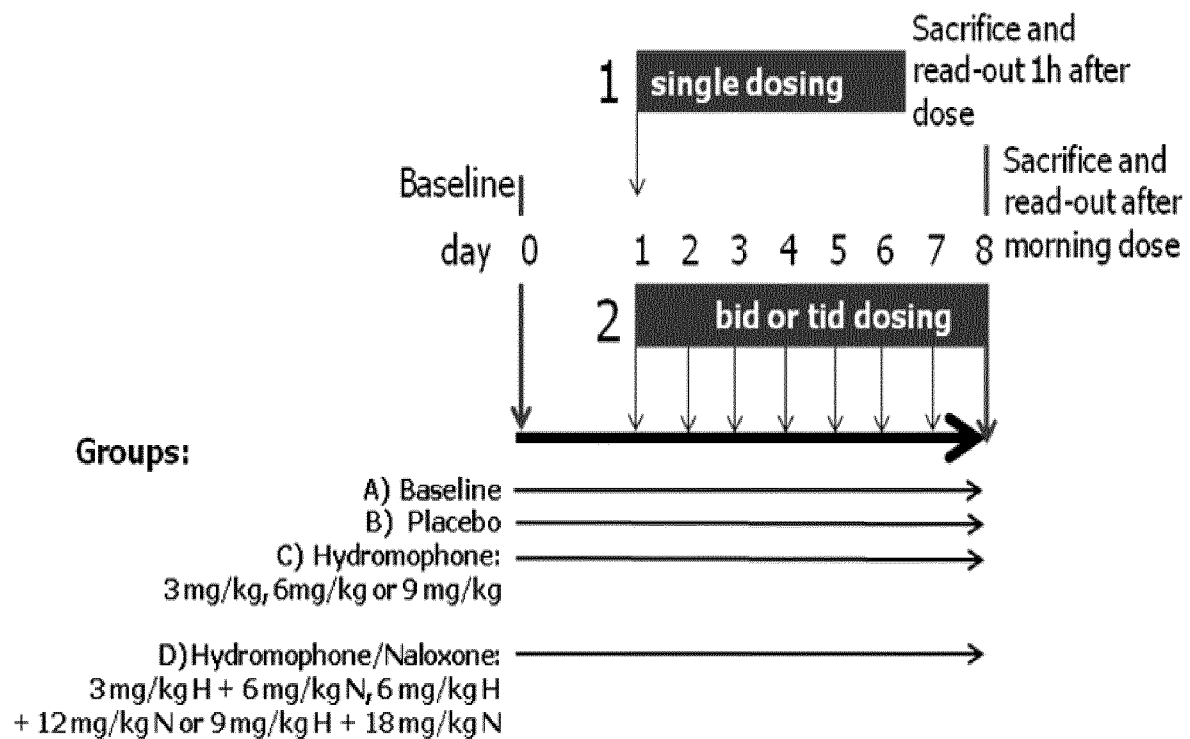
directed to the improvement of opioid-induced constipation and/or opioid-induced bowel dysfunction.

Figure 1



1/1

Figure 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/051371

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/485 A61K9/00 A61P25/04 A61K45/06 ADD.		
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 practicable, search terms used) EPO-Internal, BIOSIS, WPI Data, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	----- NIEUWENHUIJS V B ET AL: "The role of interdigestive small bowel motility in the regulation of gut microflora, bacterial overgrowth, and bacterial translocation in rats", ANNALS OF SURGERY, J.B. LIPPINCOTT COMPANY, PHILADELPHIA, US, vol. 228, no. 2, 1 August 1998 (1998-08-01), pages 188-193, XP009162973, ISSN: 0003-4932 pages 188-189; figures 2-3; table 2 page 192, paragraph 1 ----- -/--	1-15
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 9 March 2016		Date of mailing of the international search report 22/03/2016
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		Authorized officer Ansaldo, M

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/051371

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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