Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aristiga 10 mg/5 mg prolonged release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 10 mg of oxycodone hydrochloride equivalent to 9 mg oxycodone, and 5 mg naloxone hydrochloride as 5.5 mg of naloxone hydrochloride dihydrate, equivalent to 4.5 mg naloxone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White to off-white, 9.6x4.8mm, elliptic, biconvex coated tablet, engraved with “10” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe pain, which can be adequately managed only with opioid analgesics.
The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

Aristiga is indicated in adults.

4.2 Posology and method of administration

Posology

Analgesia

The analgesic efficacy of Aristiga is equivalent to oxycodone hydrochloride prolonged-release formulations.

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient. Unless otherwise prescribed, Aristiga should be administered as follows:

Adults:

The usual starting dose for an opioid naive patient is 10 mg/5 mg of oxycodone hydrochloride/naloxone hydrochloride at 12 hourly intervals.

Patients already receiving opioids may be started on higher doses of Aristiga depending on their previous opioid experience.

Aristiga 5 mg/2.5 mg is intended for dose titration when initiating opioid therapy and individual dose adjustment.

The maximum daily dose of these tablets is 160 mg oxycodone hydrochloride and 80 mg naloxone hydrochloride. The maximum daily dose is reserved for patients who have previously been maintained on a stable daily dose and who have become in need of an increased dose. Special attention should be given to patients with compromised renal function and patients with mild hepatic impairment if an increased dose is considered. For patients requiring higher doses,

administration of supplemental prolonged-release oxycodone hydrochloride at the same time intervals should be considered, taking into account the maximum daily dose of 400 mg prolonged-release oxycodone hydrochloride. In the case of supplemental oxycodone hydrochloride dosing, the beneficial effect of naloxone hydrochloride on bowel function may be impaired.

After complete discontinuation of therapy with these tablets with a subsequent switch to another opioid a worsening of the bowel function can be expected.

Some patients taking these prolonged-release tablets according to a regular time schedule require immediate-release analgesics as “rescue” medication for breakthrough pain. Aristiga is a prolonged-release formulation and therefore not intended for the treatment of breakthrough pain. For the treatment of breakthrough pain, a single dose of “rescue medication” should approximate one sixth of the equivalent daily dose of oxycodone hydrochloride. The need for more than two “rescues” per day is usually an indication that the dosage requires upward adjustment. This adjustment should be made every 1-2 days in steps of 5 mg/2.5 mg twice daily, or where demanded 10 mg/5 mg, oxycodone hydrochloride/naloxone hydrochloride until a stable dose is reached. The aim is to establish a patient-specific twice daily dose that will maintain adequate analgesia and make use of as little rescue medication as possible for as long as pain therapy is necessary.

Aristiga is taken at the determined dosage twice daily according to a fixed time schedule. While symmetric administration (the same dose mornings and evenings) subject to a fixed time schedule (every 12 hours) is appropriate for the majority of patients, some patients, depending on the individual pain situation, may benefit from asymmetric dosing tailored to their pain pattern. In general, the lowest effective analgesic dose should be selected.

In non-malignant pain therapy, daily doses of up to 40 mg/20 mg oxycodone hydrochloride/naloxone hydrochloride are usually sufficient, but higher doses may be needed.

For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

Elderly
As for younger adults the dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

Hepatic impairment
A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic impairment. Naloxone concentrations were affected to a higher degree than oxycodone (see section 5.2). The clinical relevance of a relative high naloxone exposure in hepatic impaired patients is yet not known. Caution must be exercised when administering these tablets to patients with mild hepatic impairment (see section 4.4). In patients with moderate and severe hepatic impairment Aristiga is contraindicated (see section 4.3).

Renal impairment

A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment (see section 5.2). Naloxone concentrations were affected to a higher degree than oxycodone. The clinical relevance of a relative high naloxone exposure in renal impaired patients is yet not known. Caution should be exercised when administering these tablets to patients with renal impairment (see section 4.4).

Paediatric population

The safety and efficacy of Aristiga in children and adolescents aged below 18 years has not been established. No data are available.

Method of administration

Oral use.

These prolonged-release tablets are taken in the determined dosage twice daily in a fixed time schedule.

The prolonged-release tablets may be taken with or without food with sufficient liquid. These tablets must be swallowed whole, and not broken, chewed or crushed (see section 4.4).

Duration of use

These tablets should not be administered for longer than absolutely necessary.
If long-term pain treatment is necessary in view of the nature and severity of the illness, careful and regular monitoring is required to establish whether and to what extent further treatment is necessary.

When a patient no longer requires opioid therapy cessation of treatment by tapering down over a period of approximately one week is recommended in order to reduce the risk of a withdrawal reaction (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1,
- Severe respiratory depression with hypoxia and/or hypercapnia,
- Severe chronic obstructive pulmonary disease,
- Cor pulmonale,
- Severe bronchial asthma,
- Non-opioid induced paralytic ileus,
- Moderate to severe hepatic impairment.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression.
Caution must be exercised when administering these tablets to elderly or infirm patients, patients with opioid-induced paralytic ileus, patients presenting severely impaired pulmonary function, myxoedema, hypothyroidism, Addison's disease (adrenal cortical insufficiency), toxic psychosis, cholelithiasis, prostate hypertrophy, alcoholism, delirium tremens, pancreatitis, hypotension, hypertension, pre-existing cardiovascular diseases, head injury (due to the risk of increased intracranial pressure), epileptic disorder or predisposition to convulsions, or patients taking MAO inhibitors.

Caution must also be exercised when administering these tablets to patients with mild hepatic or renal impairment. Careful medical monitoring is particularly necessary for patients with severe renal impairment.

Diarrhoea may be considered as a possible effect of naloxone.

In patients under long-term opioid treatment the switch to Aristiga can initially provoke withdrawal symptoms. Such patients may require specific attention.

Aristiga is not suitable for the treatment of withdrawal symptoms.

During long-term administration, the patient may develop tolerance to the medicinal product and require higher doses to maintain the desired effect. Chronic administration of these tablets may lead to physical dependence. Withdrawal symptoms may occur upon the abrupt cessation of therapy. If therapy is no longer required, it may be advisable to reduce the daily dose gradually in order to avoid the occurrence of withdrawal syndrome (see section 4.2).

There is potential for development of psychological dependence (addiction) to opioid analgesics, including Aristiga. These tablets should be used with particular care in patients with a history of alcohol and drug abuse. Oxycodone alone has an abuse profile similar to other strong agonist opioids.

In order not to impair the prolonged-release characteristic of the prolonged-release tablets, the prolonged-release tablets must be taken whole and must not be broken, chewed or crushed. Breaking, chewing or crushing the prolonged-release tablets for ingestion leads to a faster release of the active substances and the absorption of a possibly fatal dose of oxycodone (see section 4.9).

Concomitant use of alcohol and Aristiga may increase the undesirable effects of Aristiga; concomitant use should be

avoided.

Studies have not been performed on the safety and efficacy of Aristiga in children and adolescents below the age of 18 years. Therefore, their use in children and adolescents under 18 years of age is not recommended.

There is no clinical experience in patients with cancer associated to peritoneal carcinomatosis or with sub-occlusive syndrome in advanced stages of digestive and pelvic cancers. Therefore, the use of these tablets in this population is not recommended.

These tablets arenot recommended for pre-operative use or within the first 12-24 hours post-operatively. Depending on the type and extent of surgery, the anaesthetic procedure selected, other co-medication and the individual condition of the patient, the exact timing for initiating post-operative treatment with these tablets depends on a careful risk-benefit assessment for each individual patient.

Any abuse of these tablets by drug addicts is strongly discouraged.

If abused parenterally, intranasally or orally by individuals dependent on opioid agonists, such as heroin, morphine, or methadone, these tablets are expected to produce marked withdrawal symptoms - because of the opioid receptor antagonist characteristics of naloxone - or to intensify withdrawal symptoms already present (see section 4.9).

These tablets consist of a dual-polymer matrix, intended for oral use only. Abusive parenteral injections of the prolonged-release tablet constituents (especially talc) can be expected to result in local tissue necrosis and pulmonary granulomas or may lead to other serious, potentially fatal undesirable effects.

The empty prolonged-release tablet matrix may be visible in the stool.

The use of Aristiga may produce positive results in doping controls. The use of Aristiga as a doping agent may become a health hazard.

4.5 Interaction with other medicinal products and other forms of interaction

Substances having a CNS-depressant effect (e.g. other opioids, sedatives, hypnotics, antidepressants, phenothiazines, neuroleptics, anti-histamines and anti-emetics) may enhance the CNS-depressant effect (e.g. respiratory depression) of Aristiga.

Alcohol may enhance the pharmacodynamic effects of Aristiga, concomitant use should be avoided.

Clinically relevant changes in International Normalized Ratio (INR or Quick-value) in both directions have been observed in individuals if oxycodone and coumarin anticoagulants are co-applied.

Oxycodone is metabolised primarily via the CYP3A4 pathways and partly via the CYP2D6 pathway (see section 5.2). The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements. Aristiga doses may need to be adjusted accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin, telithromycin), azole-antifungal agents (e.g. ketoconazole, voriconazole, itraconazole, posaconazole), protease inhibitors (e.g. ritonavir, indinavir, nelfinavir, saquinavir), cimetidine and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A reduction in the dose of these tablets and subsequent re-titration may be necessary.

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St. John's Wort, may induce the metabolism of oxycodone and cause increased clearance of the drug, resulting in a decrease in oxycodone plasma concentrations. Caution is advised and further titration may be necessary to reach an adequate level of symptom control.

Theoretically, medicinal products that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

Concomitant administration with CYP2D6 inhibitors had an insignificant effect on the elimination of oxycodone and also had no influence on the pharmacodynamic effects of oxycodone.

In vitro metabolism studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. The likelihood of clinically relevant interactions between paracetamol, acetylsalicylic acid or naltrexone and the combination of oxycodone and naloxone in therapeutic concentrations is minimal.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Aristiga in pregnant women and during childbirth. Limited data on the use of oxycodone during pregnancy in humans reveal no evidence of an increased risk of congenital abnormalities. For naloxone, insufficient clinical data on exposed pregnancies are available. However, systemic exposure of the women to naloxone after use of these tablets is relatively low (see section 5.2). Both oxycodone and naloxone pass into the placenta. Animal studies have not been performed with oxycodone and naloxone in combination (see section 5.3). Animal studies with oxycodone or naloxone administered as single drugs have not revealed any teratogenic or embryotoxic effects.

Long-term administration of oxycodone during pregnancy may lead to withdrawal symptoms in the newborn. If administered during childbirth, oxycodone may evoke respiratory depression in the newborn.

These tablets should only be used during pregnancy if the benefit outweighs the possible risks to the unborn child or neonate.

Breast-feeding

Oxycodone passes into the breast milk. A milk-plasma concentration ratio of 3.4:1 was measured and oxycodone effects in the suckling infant are therefore conceivable. It is not known whether naloxone also passes into the breast milk. However, after taking these tablets systemic naloxone levels are very low (see section 5.2).

A risk to the suckling child cannot be excluded in particular following intake of multiple doses of these tablets by the breastfeeding mother.

Breastfeeding should be discontinued during treatment with Aristiga.

Fertility

There are no data with respect to fertility.

4.7 Effects on ability to drive and use machines

Aristiga has moderate influence on the ability to drive and use machines. This is particularly likely at the beginning of treatment, after dose increase or product rotation and if these tablets are combined with other CNS depressant agents. Patients stabilised on a specific dosage will not necessarily be restricted. Therefore, patients should consult with their physician as to whether driving or the use of machinery is permitted.

4.8 Undesirable effects

The following frequencies are the basis for assessing undesirable effects:

Term	Frequency
Very common:	≥ 1/10
Common:	≥ 1/100 to < 1/10
Uncommon:	≥ 1/1,000 to < 1/100
Rare:	≥ 1/10,000 to < 1/1,000

Very rare:	< 1/10,000
Not known	(cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Undesirable effects in the treatment of pain

System organ class MedDRA	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders		Hypersensitivity			
Metabolism and nutrition disorders	Decreased appetite up to loss of appetite				
Psychiatric disorders	Insomnia	Abnormal thinking, Anxiety, Confusional state, Depression, Libido decreased, Nervousness, Restlessness			Euphoric mood, Hallucination, Nightmares
Nervous system disorders	Dizziness, Headache, Somnolence	Convulsions[1], Disturbance in attention, Dygeusia, Speech disorder, Syncope, Tremor, Lethargy			Paraesthesia, Sedation
Eye disorders		Visual impairment			
Ear and labyrinth disorders	Vertigo				
Cardiac disorders		Angina pectoris[2], Palpitations	Tachycardia		
Vascular disorders	Hot flush	Blood pressure decreased, Blood pressure increased			
Respiratory, thoracic and mediastinal disorders		Dyspnoea, Rhinorrhoea, Cough	Yawning		Respiratory depression
Gastrointestinal disorders	Abdominal pain, Constipation, Diarrhoea,	Abdominal distention	Tooth disorder		Eructation

	Dry mouth, Dyspepsia, Vomiting, Nausea, Flatulence				
Hepatobiliary disorders		Hepatic enzymes increased, Biliary colic			
Skin and subcutaneous tissue disorders	Pruritus, Skin reactions, Hyperhydrosis				
Musculoskeletal and connective tissue disorders		Muscle spams, Muscle twitching, Myalgia			
Renal and urinary disorders		Micturition urgency			Urinary retention
Reproductive system and breast disorders					Erectile dysfunction
General disorders and administration site conditions	Asthenia, Fatigue	Chest pain, Chills, Drug withdrawal syndrome, Malaise, Pain, Peripheral oedema, Thirst			
Investigations		Weight decreased	Weight increased		
Injury, poisoning and procedural complications		Injury from accidents			

[1] particulary in persons with epileptic disorder or predisposition to convulsions

[2] in particular in patients with history of coronary artery disease

For the active substance oxycodone hydrochloride, the following additional undesirable effects are known:

Due to its pharmacological properties, oxycodone hydrochloride may cause respiratory depression, miosis, bronchial spam and spasms of nonstriated muscles as well as suppress the cough reflex.

System organ class MedDRA	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations			Herpes simplex		
Immune					Anaphylactic

system disorders					responses
Metabolism and nutritional disorders		Dehydration	Increased appetite		
Psychiatric disorders	Altered mood and personality change, Decreased activity, Psychomotor hyperactivity	Agitation, Perception disturbances (e.g. derealisation), Drug dependence			Aggression
Nervous system disorders		Concentration impaired, Migraine, Hypertonia, Involuntary muscle contractions, Hypoaesthesia, Abnormal co-ordination			Hyperalgesia
Ear and labyrinth disorders		Hearing impaired			
Vascular disorders		Vasodilatation			
Respiratory, thoracic and mediastinal disorders		Dysphonia			
Gastrointestinal disorders	Hiccups	Dysphagia, Ileus, Mouth ulceration, Stomatitis	Melaena, Gingival bleeding		Dental caries
Hepatobiliary disorders					Cholestasis
Skin and subcutaneous tissue disorder		Dry skin	Urticaria		
Renal and urinary disorders	Dysuria				
Reproductive system and breast disorders		Hypogonadism			Amenorrhoea
General disorders and application site conditions		Oedema, Drug tolerance			Drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of intoxication
Depending on the history of the patient, an overdose of Aristiga may be manifested by symptoms that are either triggered by oxycodone (opioid receptor agonist) or by naloxone (opioid receptor antagonist).
Symptoms of oxycodone overdose include miosis, respiratory depression, somnolence progressing to stupor, hypotonia, bradycardia as well as hypotension. Coma, non-cardiogenic pulmonary oedema and circulatory failure may occur in more severe cases and may lead to a fatal outcome.

Symptoms of a naloxone overdose alone are unlikely.

Therapy of intoxication
Withdrawal symptoms due to an overdose of naloxone should be treated symptomatically in a closely-supervised environment.

Clinical symptoms suggestive of an oxycodone overdose may be treated by the administration of opioid antagonists (e.g. naloxone hydrochloride 0.4-2 mg intravenously). Administration should be repeated at 2-3 minute intervals, as clinically necessary. It is also possible to apply an infusion of 2 mg naloxone hydrochloride in 500 ml of 0.9% sodium chloride or 5% dextrose (0.004 mg/ml naloxone). The infusion should be run at a rate aligned to the previously administered bolus doses and to the patient's response.

Consideration may be given to gastric lavage.

Supportive measure (artificial ventilation, oxygen, vasopressors and fluid infusions) should be employed as necessary, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary. Fluid and electrolyte metabolism should be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; Opioids; Natural opium alkaloids.
ATC code: N02A A55.

Mechanism of action
Oxycodone and naloxone have an affinity for kappa, mu and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). Oxycodone acts as opioid-receptor agonist at these receptors and binds to the endogenous opioid receptors in the CNS. By contrast, naloxone is a pure antagonist acting on all types of opioid receptors.

Pharmacodynamic effects
Because of the pronounced first-pass metabolism, the bioavailability of naloxone upon oral administration is <3%, therefore a clinically relevant systemic effect is unlikely. Due to the local competitive antagonism of the opioid receptor mediated oxycodone effect by naloxone in the gut, naloxone reduces the bowel function disorders that are typical for opioid treatment.

Clinical efficacy and safety
Opioids can influence the hypothalamic-pituitary-adrenal or gonadal axes. Among the changes observed are an increase

of prolactin in the serum and a reduced level of cortisol and testosterone in the plasma. Clinical symptoms may occur because of these hormone changes.

Preclinical studies show differing effects of natural opioids on components of the immune system. The clinical significance of these findings is not known. It is not known whether oxycodone, a semi-synthetic opioid, has similar effects on the immune system to natural opioids.

Analgesia

In a 12 weeks parallel group double-blinded study in 322 patients with opioid-induced constipation, patients who were treated with oxycodone hydrochloride-naloxone hydrochloride had on average one extra complete spontaneous (without laxatives) bowel movement in the last week of treatment, compared to patients who continued using similar doses of oxycodone hydrochloride prolonged release tablets ($p<0.0001$). The use of laxatives in the first four weeks was significantly lower in the oxycodone-naloxone group compared to the oxycodone monotherapy group (31% versus 55%, respectively, $p<0.0001$). Similar results were shown in a study with 265 non-cancer patients comparing daily doses of oxycodone hydrochloride-naloxone hydrochloride of 60 mg/30 mg to up to 80 mg/40 mg with oxycodone hydrochloride monotherapy in the same dose range.

5.2 Pharmacokinetic properties

Oxycodone hydrochloride

Absorption

Oxycodone has a high absolute bioavailability of up to 87% following oral administration.

Distribution

Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein.

Oxycodone crosses the placenta and may be detected in breast milk.

Biotransformation

Oxycodone is metabolized in the gut and the liver to noroxycodone and oxymorphone and to various glucuronide conjugates. Noroxycodone, oxymorphone and noroxymorphone are produced via the cytochrome P450 system. Quinidine reduces the production of oxymorphone in man without substantially influencing the pharmacodynamics of oxycodone. The contribution of the metabolites to overall pharmacodynamic effect is insignificant.

Elimination

Oxycodone and its metabolites are excreted in both urine and faeces.

Naloxone hydrochloride

Absorption

Following oral administration, naloxone has a very low systemic availability of <3%.

Distribution

Naloxone passes into the placenta. It is not known, whether naloxone also passes into breast milk.

Biotransformation and elimination

After parenteral administration, the plasma half-life is approximately one hour. The duration of action depends upon the dose and route of administration, intramuscular injection producing a more prolonged effect than intravenous doses. It is metabolised in the liver and excreted in the urine. The principal metabolites are naloxone glucuronide, 6β-Naloxol and its glucuronide.

Oxycodone hydrochloride / naloxone hydrochloride combination (Aristiga)

Pharmacokinetic/pharmacodynamic relationships

The pharmacokinetic characteristics of oxycodone from Aristiga are equivalent to those of prolonged-release oxycodone hydrochloride tablets administered together with prolonged-release naloxone hydrochloride tablets.

All dosage strengths of Aristiga are interchangeable.

After the oral administration of Aristiga in maximum dose to healthy subjects, the plasma concentrations of naloxone are so low that it is not feasible to carry out a pharmacokinetic analysis. To conduct a pharmacokinetic analysis naloxone-3-glucuronide as surrogate marker is used, since its plasma concentration is high enough to measure.

Overall, following ingestion of a high-fat breakfast, the bioavailability and peak plasma concentration (Cmax) of oxycodone were increased by an average of 16% and 30% respectively compared to administration in the fasting state. This was evaluated as clinically not relevant, therefore Aristiga prolonged-release tablets may be taken with or without food (see section 4.2).

In vitro drug metabolism studies have indicated that the occurrence of clinically relevant interactions involving Aristiga is unlikely.

Elderly

Oxycodone
For AUCτ of oxycodone, on average there was an increase to 118% (90% C.I.: 103, 135), for elderly compared with younger volunteers. For Cmax of oxycodone, on average there was an increase to 114% (90% C.I.: 102, 127). For Cmin of oxycodone, on average there was an increase to 128% (90% C.I.: 107, 152).

Naloxone
For AUCτ of naloxone, on average there was an increase to 182% (90% C.I.: 123, 270), for elderly compared with younger volunteers. For Cmax of naloxone, on average there was an increase to 173% (90% C.I.: 107, 280). For Cmin of naloxone, on average there was an increase to 317% (90% C.I.: 142, 708).

Naloxone-3-glucuronide
For AUCτ of naloxone-3-glucuronide, on average there was an increase to 128% (90% C.I.: 113, 147), for elderly compared with younger volunteers. For Cmax of naloxone-3-glucuronide, on average there was an increase to 127% (90% C.I.: 112, 144). For Cmin of naloxone-3-glucuronide, on average there was an increase to 125% (90% C.I.: 105, 148).

Hepatic impairment

Oxycodone
For AUCINF of oxycodone, on average there was an increase to 143% (90% C.I.: 111, 184), 319% (90% C.I.: 248, 411) and 310% (90% C.I.: 241, 398) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For Cmax of oxycodone, on average there was an increase to 120% (90% C.I.: 99, 144), 201% (90% C.I.: 166, 242) and 191% (90% C.I.: 158, 231) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2Z}$ of oxycodone, on average there was an increase to 108% (90% C.I.: 70, 146), 176% (90% C.I.: 138, 215) and 183% (90% C.I.: 145, 221) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Naloxone
For AUCt of naloxone, on average there was an increase to 411% (90% C.I.: 152, 1112), 11518% (90% C.I.: 4259, 31149) and 10666% (90% C.I.: 3944, 28847) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For Cmax of naloxone, on average there was an increase to 193% (90% C.I.: 115, 324), 5292% (90% C.I: 3148, 8896) and 5252% (90% C.I.: 3124, 8830) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. Due to insufficient amount of data available $t_{1/2Z}$ and the corresponding AUC_{INF} of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUC_t values.

Naloxone-3-glucuronide
For AUCINF of naloxone-3-glucuronide, on average there was an increase to 157% (90% C.I.: 89, 279), 128% (90%

C.I.: 72, 227) and 125% (90% C.I.: 71, 222) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For Cmax of naloxone-3-glucuronide, on average there was an increase to 141% (90% C.I.: 100, 197), 118% (90% C.I.: 84, 166) and a decrease to 98% (90% C.I.: 70, 137) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2Z}$ of naloxone-3-glucuronide, on average there was an increase to 117% (90% C.I.: 72, 161), a decrease to 77% (90% C.I.: 32, 121) and a decrease to 94% (90% C.I.: 49, 139) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Renal impairment

Oxycodone
For AUCINF of oxycodone, on average there was an increase to 153% (90% C.I.: 130, 182), 166% (90% C.I.: 140, 196) and 224% (90% C.I.: 190, 266) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For Cmax of oxycodone, on average there was an increase to 110% (90% C.I.: 94, 129), 135% (90% C.I.: 115, 159) and 167% (90% C.I.: 142, 196) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2Z}$ of oxycodone, on average there was an increase to 149%, 123% and 142% for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

Naloxone
For AUCt of naloxone, on average there was an increase to 2850% (90% C.I.: 369, 22042), 3910% (90% C.I.: 506, 30243) and 7612% (90% C.I.: 984, 58871) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For Cmax of naloxone, on average there was an increase to 1076% (90% C.l.: 154, 7502), 858% (90% C.I.: 123, 5981) and 1675% (90% C.I.: 240, 11676) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. Due to insufficient amount of data available $t_{1/2Z}$ and the corresponding AUCINF of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUCt values. The ratios may have been influenced by the inability to fully characterize the naloxone plasma profiles for the healthy subjects.

Naloxone-3-glucuronide
For AUCINF of naloxone-3-glucuronide, on average there was an increase to 220% (90% C.I.: 148, 327), 370% (90% C.I.: 249, 550) and 525% (90% C.I.: 354, 781) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects. For Cmax of naloxone-3-glucuronide, on average there was an increase to 148% (90% C.I.: 110, 197), 202% (90% C.I.: 151, 271) and 239% (90% C.I.: 179, 320) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects. For $t_{1/2Z}$ of naloxone-3-glucuronide, on average there was no significant change between the renally impaired subjects and the healthy subjects.

Abuse
To avoid damage to the prolonged-release properties of the tablets, Aristiga must not be broken, crushed or chewed, as this leads to a rapid release of the active substances. In addition, naloxone has a slower elimination rate when administered intranasally. Both properties mean that abuse of Aristiga will not have the effect intended. In oxycodone-dependent rats, the intravenous administration of oxycodone hydrochloride / naloxone hydrochloride at a ratio of 2:1 resulted in withdrawal symptoms.

5.3 Preclinical safety data

There are no data from studies on reproductive toxicity of the combination of oxycodone and naloxone. Studies with the single components showed that oyxcodone had no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformations in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual foetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the pregnant animals. In a study on pre- and postnatal development in rats F1 body weights were lower at 6 mg/kg/d when compared to body weights of the control group at doses which reduced maternal weight and food intake

(NOAEL 2 mg/kg body weight). There were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices. The standard oral reproduction toxicity studies with naloxone show that at high oral doses naloxone was not teratogenic and/or embryo/foetotoxic, and does not affect perinatal/postnatal development. At very high doses (800 mg/kg/day) naloxone produced increased pup deaths in the immediate post-partum period at dosages that produced significant toxicity in maternal rats (e.g. body weight loss, convulsions). However, in surviving pups, no effects on development or behaviour were observed.

Long-term carcinogenicity studies with oxycodone/naloxone in combination or oxycodone as a single entity have not been performed. For naloxone, a 24-months oral carcinogenicity study was performed in rats with naloxone doses up to 100 mg/kg/day. The results indicate that naloxone is not carcinogenic under these conditions.

Oxycodone and naloxone as single entities show a clastogenic potential in *in vitro* assays. No similar effects were observed, however, under *in vivo* conditions, even at toxic doses. The results indicate that the mutagenic risk of Aristiga to humans at therapeutic concentrations may be ruled out with adequate certainty.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Hypromellose
Polyvinyl acetate
Povidone
Sodium laurilsulfate
Cellulose microcrystalline
Silicon dioxide
Colloidal anhydrous silica
Magnesium stearate.

Tablet coat:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Peelable, child resistant perforated unit dose blister: Polyamide-Aluminium-PVC / Aluminium-PET foil blister.

Pack sizes:
10x1, 14x1, 20x1, 28x1, 30x1, 50x1, 56x1, 60x1, 98x1, 100x1, and 100x1 (Hospital pack) prolonged release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ethypharm SA
194 Bureaux de la Colline, Bâtiment D
92213 Saint-Cloud cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0549/017/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th March 2017

10 DATE OF REVISION OF THE TEXT