Package leaflet: Information for the user

Aristiga 5 mg/2.5 mg prolonged-release tablets
Aristiga 10 mg/5 mg prolonged-release tablets
Aristiga 20 mg/10 mg prolonged-release tablets
Aristiga 40 mg/20 mg prolonged-release tablets

oxycodone hydrochloride / naloxone hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Aristiga is and what it is used for

Aristiga is a prolonged-release tablet, which means that its active substances are released over an extended period. Their action lasts for 12 hours.

These tablets are only for use in adults.

Pain relief
You have been prescribed Aristiga for the treatment of severe pain, which can be adequately managed only with opioid analgesics. Naloxone hydrochloride is added to counteract constipation.

How these tablets work in pain relief
These tablets contain oxycodone hydrochloride and naloxone hydrochloride as active substances. Oxycodone hydrochloride is responsible for the pain-killing effect of Aristiga, and is a potent analgesic (“painkiller”) of the opioid group. The second active substance of Aristiga, naloxone hydrochloride, is intended to counteract constipation. Bowel dysfunction (e.g. constipation) is a typical side effect of treatment with opioid painkillers.

2. What you need to know before you take Aristiga

Do not take Aristiga:
- if you are allergic to oxycodone hydrochloride, naloxone hydrorochloride or any of the other ingredients of this medicine (listed in section 6),
- if your breathing is not able to supply enough oxygen to the blood, and get rid of carbon dioxide produced in the body (respiratory depression),
- if you suffer from a severe lung disease associated with narrowing of the airways (chronic obstructive pulmonary disease or COPD),

- if you suffer from a condition known as cor pulmonale. In this condition the right side of the heart becomes enlarged, due to increased pressure inside blood vessels in the lung etc (e.g. as a result of COPD – see above),
- if you suffer from severe bronchial asthma,
- if you have paralytic ileus (a type of bowel obstruction) not caused by opioids,
- if you have moderate to severe liver dysfunction.

Warnings and precautions

Talk to your doctor or pharmacist before taking Aristiga:
- in the case of elderly patients or debilitated (weak) patients,
- if you have paralytic ileus (a type of bowel obstruction) caused by opioids,
- if you have kidney impairment,
- if you have mild liver impairment,
- if you have severe lung impairment (i.e. reduced breathing capacity),
- if you have myxoedema (a thyroid disorder, with dryness, coldness and swelling [‘puffiness’] of the skin, affecting the face and limbs),
- if your thyroid gland is not producing enough hormones (underactive thyroid, or hypothyroidism),
- if your adrenal glands are not producing enough hormones (adrenal insufficiency, or Addison’s disease),
- if you have a mental illness accompanied by a (partial) loss of reality (psychosis), due to alcohol or intoxication with other substances (substance-induced psychosis),
- if you suffer from gallstone problems,
- if your prostate gland is abnormally enlarged (prostate hypertrophy),
- if you suffer from alcoholism or delirium tremens,
- if your pancreas is inflamed (pancreatitis),
- if you have low blood pressure (hypotension),
- if you have high blood pressure (hypertension),
- if you have pre-existing cardiovascular disease,
- if you have a head injury (due to the risk of increased brain pressure),
- if you suffer from epilepsy or are prone to seizures,
- if you are also taking MAO inhibitors (used to treat depression or Parkinson’s disease), e.g. medicines containing tranylcypromine, phenelzine, isocarboxazid, moclobemide and linezolid.

Tell your doctor if any of the above has ever applied to you in the past. Also, please tell your doctor if you develop any of the above disorders while you are taking these tablets. The most serious result of opioid overdose is respiratory depression (slow and shallow breathing). This may also cause blood oxygen levels to fall, resulting in possible fainting, etc.

You must swallow the prolonged-release tablet whole, so as not to affect the slow release of oxycodone hydrochloride from the prolonged-release tablet. Do not break, chew or crush the tablets. Taking broken, chewed or crushed tablets may lead to the absorption of a potentially lethal dose of oxycodone hydrochloride (see section 3 “If you take more Aristiga than you should”).

If you experience severe diarrhoea at the start of treatment, this may be due to the effect of naloxone. It may be a sign that bowel function is returning to normal. Such diarrhoea can occur within the first 3-5 days of treatment. If diarrhoea should persist after 3-5 days, or give you cause for concern, please contact your doctor.

If you have been using another opioid, withdrawal symptoms may occur when you initially switch to Aristiga treatment, e.g. restlessness, bouts of sweating and muscle pain. If you experience such symptoms, you may need to be specially monitored by your doctor.

If taken over the long term, you may become tolerant to these tablets. This means you may need a higher dose to achieve the desired effect. Also, long-term use may lead to physical dependence. Withdrawal symptoms may occur if treatment is stopped too suddenly (restlessness, bouts of sweating, muscle pain). If you no longer need treatment, you should reduce your daily dose gradually, in consultation with your doctor.

The active substance oxycodone hydrochloride alone has an abuse profile similar to other strong opioids (strong analgesics). There is potential for development of psychological dependence. Oxycodone hydrochloride containing products should be avoided in patients with a present or past abuse of alcohol, drugs or medicines.

Tell your doctor in case you have cancer associated to peritoneal metastases or beginning bowel obstruction in advanced stages of digestive and pelvic cancers.
If you need to undergo surgery, please tell your doctors that you are taking Aristiga.

You may notice remnants of the prolonged-release tablet in your stools. Do not be alarmed, as the active substances (oxycodone hydrochloride and naloxone hydrochloride) have already been released in the stomach and gut, and absorbed into your body.

Incorrect use of Aristiga

These tablets are not suitable for withdrawal treatment.

Aristiga should never be abused, particularly if you have a drug addiction. If you are addicted to substances such as heroin, morphine or methadone, severe withdrawal symptoms are likely if you abuse these tablets because they contain the ingredient naloxone. Pre-existing withdrawal symptoms may be made worse.

You should never misuse these tablets by dissolving and injecting them (e.g. into a blood vessel). In particular, they contain talc, which can cause destruction of local tissue (necrosis) and changes in lung tissue (lung granuloma). Such abuse can also have other serious consequences and may even be fatal.

The use of Aristiga may produce positive results in doping controls.

The use of Aristiga as a doping agent may become a health hazard.

Other medicines and Aristiga

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you take these tablets at the same time as you take other medicines, the effect of these tablets or the other medicine may be changed. Tell your doctor if you are taking:
- other potent painkillers (opioids);
- sleep medication and tranquilisers (sedatives, hypnotics);
- medicines to treat depression;medicines used to treat allergies, travel sickness or nausea (antihistamines or antiemetics);
- medicines to treat psychiatric or mental disorders (phenothiazines, neuroleptics, antipsychotics);
- medicines that decrease the blood’s clotting ability (coumarin derivatives), this clotting time may be speeded up or slowed down;
- antibiotics of the macrolide type (such as clarithromycin, erythromycin or telithromycin);
- antifungal medicines of the –azole type (e.g. ketoconazole, voriconazole, itraconizole or posaconizole);
- a specific type of medicine known as a protease inhibitor used to treat HIV (examples include ritonavir indinavir, nelfinavir or saquinavir);
- cimetidine (a medicine for stomach ulcers, indigestion or heartburn);

- rifampicin (used to treat tuberculosis);
- carbamazepine (used to treat seizures, fits or convulsions and certain pain conditions);
- phenytoin (used to treat seizures, fits or convulsions);
- a herbal remedy called St John's Wort (also known as Hypericum perforatum);
- quinidine (a medicine to treat an irregular heartbeat).

No interactions are expected between Aristiga and paracetamol, acetylsalicylic acid or naltrexone.

Aristiga with food, drink and alcohol

Drinking alcohol whilst taking Aristiga may make you feel more sleepy or increase the risk of serious side effects such as shallow breathing with a risk of stopping breathing, and loss of consciousness. It is recommended not to drink alcohol while you're taking Aristiga.

You should avoid drinking grapefruit juice while you are taking these tablets.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

Use of these tablets should be avoided to the extent possible during pregnancy. If used over prolonged periods during pregnancy, oxycodone hydrochloride may lead to withdrawal symptoms in newborn infants. If oxycodone hydrochloride is given during childbirth, respiratory depression (slow and shallow breathing) may occur in the newborn infant.

Breastfeeding

Breastfeeding should be discontinued during treatment with these tablets. Oxycodone hydrochloride passes into breast milk. It is not known whether naloxone hydrochloride also passes into breast milk. Therefore, a risk for the suckling infant cannot be excluded in particular following intake of multiple doses of Aristiga.

Driving and using machines

Aristiga may affect your ability to drive or operate machines. In particular, this is likely at the start of Aristiga, after a dose increase or after switching from a different medication. However, these side effects disappear once you are on a stable Aristiga dose.

Ask your doctor whether you may drive or operate machines.

3. How to take Aristiga

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Aristiga is a prolonged-release tablet, which means that its active substances are released over an extended period. Their action lasts for 12 hours.

You must swallow the prolonged-release tablet whole, so as not to affect the slow release of oxycodone hydrochloride from the prolonged-release tablet. Do not break, chew or crush the tablets. Taking broken, chewed or crushed tablets may lead to the absorption of a potentially lethal dose of oxycodone hydrochloride (see section 3 "If you take more Aristiga than you should").

Unless otherwise prescribed by your doctor, the usual dose is:

To treat pain

Adults

The usual starting dose is 10 mg oxycodone hydrochloride / 5 mg naloxone hydrochloride as prolonged release tablet(s) every 12 hours.

Your doctor will decide how much you should take every day and how to divide your total daily dosage into morning and evening doses. Your doctor will also decide on any necessary dose adjustments during treatment. Your dose will be adjusted according to your level of pain and individual sensitivity. You should be given the lowest dose needed for pain relief. If you have already been treated with opioids, Aristiga treatment can be started at a higher dose.

The maximum daily dose is 160 mg oxycodone hydrochloride and 80 mg naloxone hydrochloride. If you need a higher dose, your doctor may give you additional oxycodone hydrochloride without naloxone hydrochloride. However, the maximum daily dose of oxycodone hydrochloride should not exceed 400 mg. The beneficial effect of naloxone hydrochloride on bowel activity may be affected if additional oxycodone hydrochloride is given without additional naloxone hydrochloride.

If you are switched from these tablets to another opioid pain medication your bowel function will probably worsen.

If you experience pain between two doses of Aristiga, you may need a rapid-acting painkiller. Aristiga is not suitable for this. In this case, please talk to your doctor.

If you have the impression that the effect of these tablets is too strong or too weak, please talk to your doctor or pharmacist.

Elderly
In general, no dose adjustment is necessary for elderly patients with normal kidney and/or liver function.

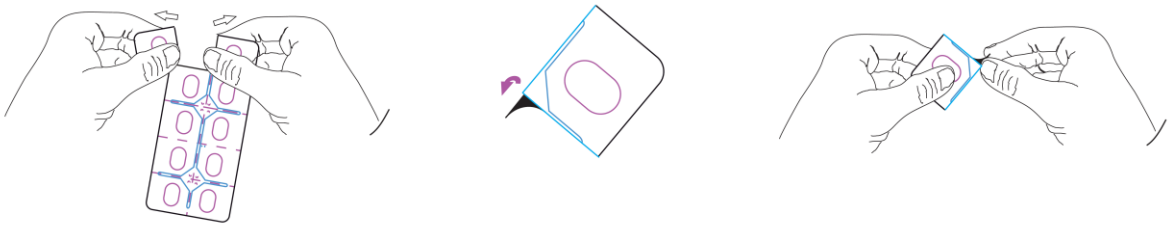
Hepatic or renal impairment
If you have an impairment of your kidney function or a mild impairment of your liver function, your attending doctor will prescribe these tablets with special caution. If you have a moderate or severe impairment of liver function, these tablets should not be used (see also Section 2 “Do not take Aristiga…” and “Warnings and precautions”).

Children and adolescents below 18 years of age
Aristiga has not yet been studied in children and adolescents under 18 years of age. Its safety and effectiveness have not been proven in children and adolescents. For this reason, Aristiga use in children and adolescents under 18 years of age is not recommended.

Method of administration
Oral use.

Swallow these tablets whole (without chewing), with sufficient liquid (½ glass of water). You can take the prolonged-release tablets with or without food. Take the tablets every 12 hours, according to a fixed time schedule (e.g. at 8 o’clock in the morning and 8 o’clock in the evening). Do not break, chew or crush the prolonged-release tablets (see section 2 “Warnings and precautions”).

Opening instructions:
This medicinal product is available in peelable, child resistant perforated unit dose blisters.



Pull off a single dose by tearing along the perforated line on the blister and peel back the foil on the blister to expose the tablet.

Duration of use
In general, you should not take these tablets for any longer than you need to. If you are on long-term treatment, your doctor should regularly check whether you still need these tablets.

If you take more Aristiga than you should
If you have taken more than the prescribed dose of these tablets you must inform your doctor immediately.

An overdose may result in:
- narrowed pupils
- slow and shallow breathing (respiratory depression)
- drowsiness up to loss of consciousness)
- low muscle tone (hypotonia)
- reduced pulse rate, and
- a drop in blood pressure.

In severe cases, loss of consciousness (coma), fluid on the lungs and circulatory collapse may occur, which may be fatal in some cases.

You should avoid situations which require a high level of alertness, e.g. driving.

If you forget to take Aristiga
Or if you take a dose lower than the one prescribed, you may not feel any effect.

If you should forget to take your dose, please follow the instructions below:
- If your next usual dose is due in 8 hours or more: Take the forgotten dose immediately and continue with your normal dosing schedule.
- If your next usual dose is due within less than 8 hours: Take the forgotten dose. Then, wait another 8 hours before taking your next dose. Try to get back on track with your original dosing schedule (e.g. 8 o'clock in the morning and 8 o'clock in the evening). Do not take more than one dose within any 8-hour period.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Aristiga

Do not stop your treatment without consulting your doctor.

If you do not require any further treatment, you must reduce the daily dose gradually after talking to your doctor. In this way, you will avoid withdrawal symptoms, such as restlessness, bouts of sweating and muscle pain.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Important side effects to look out for, and what to do if you are affected:

If you are affected by any of the following important side effects, consult your nearest doctor immediately.

Slow and shallow breathing (respiratory depression) is the main danger of an opioid overdose. It mostly occurs in elderly and debilitated (weak) patients. Opioids can also cause a severe drop in blood pressure in susceptible patients.

Common (may affect up to 1 in 10 people)

- abdominal pain
- constipation
- diarrhoea
- dry mouth
- indigestion
- vomit (be sick)
- feel sick
- flatulence (wind)
- decreased appetite up to loss of appetite
- a feeling of dizziness or 'spinning'
- headache
- hot flushes
- a feeling of unusual weakness
- tiredness or exhaustion
- itchy skin
- skin reactions/rash
- sweating
- vertigo
- difficulty in sleeping
- drowsiness

Uncommon (may affect up to 1 in 100 people)

- abdominal bloating
- abnormal thoughts
- anxiety
- confusion
- depression
- nervousness
- chest tightness especially if you already have coronary heart disease
- drop in blood pressure
- withdrawal symptoms such as agitation
- fainting
- lack of energy
- thirst
- altered taste
- palpitations
- biliary colic
- chest pain
- generally feeling unwell
- pain
- swelling of hands, ankles or feet
- difficulties to concentrate
- impaired speaking
- shaking
- difficulties breathing
- restlessness
- chills
- hepatic enzymes increased
- rise in blood pressure
- reduced sexual drive
- runny nose
- cough
- hypersensitivity/ allergic reactions
- injuries from accidents
- increased urge to urinate
- muscle cramps
- muscle twitches
- muscle pain
- vision impairment
- epileptic seizures (especially in persons with epileptic disorder or predisposition to seizures)

Rare (may affect up to 1 in 1,000 people)

- increase in pulse rate
- dental changes
- weight gain
- yawning

Not known (frequency cannot be estimated from the available data)

- euphoric mood
- severe drowsiness
- erectile dysfunction
- nightmares
- hallucinations
- shallow breathing
- difficulties in passing urine
- tingling skin (pins and needles)
- belching

<u>The active substance oxycodone hydrochloride, if not combined with naloxone hydrochloride, is known to have the following differing side-effects:</u>

Oxycodone can cause breathing problems (respiratory depression), reduction in size of the pupil in the eye, cramping of the bronchial muscles and cramping of the smooth muscles, as well as depression of the cough reflex.

Common (may affect up to 1 in 10 people)

- altered mood and personality changes (e.g. depression, feeling of extreme happiness)
- decreased activity
- increased activity
- difficulties in passing urine
- hiccups

Uncommon (may affect up to 1 in 100 people)

- impaired concentration
- migraines
- increased muscle tension
- involuntary muscle contractions
- drug dependence
- a condition where the bowel stops working properly (ileus)
- dry skin
- drug tolerance
- reduced sensitivity to pain or touch
- abnormal coordination
- vocal changes (dysphonia)
- water retention
- difficulties in hearing
- mouth ulcers
- difficulties in swallowing
- sore gums
- perception disturbances (e.g. hallucination, derealisation)
- flushing of skin
- dehydration
- agitation
- a decrease in sex hormone levels which may affect sperm production in men or the menstrual cycle in females

Rare (may affect up to 1 in 1,000 people)

- itching rash (urticaria)
- infections such as cold sores or herpes (which may cause blisters around the mouth or genital area)
- increased appetite
- black (tarry) stools
- bleeding gums

Not known (frequency cannot be estimated from the available data)

- acute generalized allergic reactions (anaphylactic reactions)
- an increase in sensitivity to pain
- absence of menstrual periods
- withdrawal symptoms in the newborn
- aggression
- problems with bile flow
- tooth decay

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aristiga

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Aristiga contains

The active substances are oxycodone hydrochloride and naloxone hydrochloride.

Aristiga 5 mg/2.5 mg
Each prolonged-release tablet contains 5 mg oxycodone hydrochloride, equivalent to 4.5 mg oxycodone, and 2.5 mg naloxone hydrochloride as 2.75 mg naloxone hydrochloride dihydrate, equivalent to 2.25 mg naloxone.

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

Aristiga 20 mg/10 mg
Each prolonged-release tablet contains 20 mg oxycodone hydrochloride, equivalent to 18 mg oxycodone, and 10 mg naloxone hydrochloride as 11.0 mg naloxone hydrochloride dihydrate, equivalent to 9.01 mg naloxone.

Aristiga 40 mg/20 mg
Each prolonged-release tablet contains 40 mg oxycodone hydrochloride, equivalent to 36 mg oxycodone, and 20 mg naloxone hydrochloride as 22 mg naloxone hydrochloride dihydrate, equivalent to 18.02 mg naloxone.

The other ingredients are:

Tablet core:
hypromellose, polyvinyl acetate, povidone, sodium laurilsulfate, cellulose microcrystalline, silicon dioxide, colloidal anhydrous silica, magnesium stearate.

Aristiga 5 mg/2.5 mg
Tablet coat:
polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, brillant blue FCF aluminum lake (E133)

Aristiga 10 mg/5 mg
Tablet coat:
polyvinyl alcohol, titanium dioxide, macrogol 3350, talc

Aristiga 20 mg/10 mg
Tablet coat:
polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, red iron oxide (E172), yellow iron oxide (E172)

Aristiga 40 mg/20 mg
Tablet coat:
polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, red iron oxide (E172) , yellow iron oxide (E172), black iron oxide (E172)

What Aristiga looks like and contents of the pack
Prolonged-release tablet.

Aristiga 5 mg/2.5 mg
Blue, 9.6x4.8mm, elliptic, biconvex coated tablet, engraved with “5” on one side.

Aristiga 10 mg/5 mg

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

Aristiga 20 mg/10 mg
Pink, 9.6x4.8mm, elliptic, biconvex coated tablet, engraved with “20” on one side.

Aristiga 40 mg/20 mg
Yellow, 11x5.5mm, elliptic, biconvex coated tablet, engraved with “40” on one side.

Aristiga prolonged release tablets are available in peelable, child resistant perforated unit dose blisters of: 10x1, 14x1, 20x1, 28x1, 30x1, 50x1, 56x1, 60x1, 98x1, 100x1, 100x1 (Hospital pack) tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Ethypharm
194 Bureaux de la Colline, Bâtiment D
92213 Saint Cloud cedex
France

Manufacturer
Ethypharm
Chemin de la Poudrière
76120 Le Grand Quevilly
France

This medicinal product is authorised in the Member States of the EEA under the following names:

Germany :	Oxycodon-HCl/Naloxon-HCl Ethypharm 5 mg/2,5 mg, 10 mg/5 mg, 20 mg/10 mg and 40 mg/20 mg Retardtabletten
Ireland:	Aristiga 5 mg/2,5 mg, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg prolonged release tablets
United Kingdom	Aristiga 5 mg/2,5 mg, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg prolonged release tablet

This leaflet was last revised in {12/2016}.