SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Celastymis 80 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 80 mg oxycodone hydrochloride corresponding to 71.7 mg oxycodone.
Excipients with known effect:
Each prolonged-release tablet contains 60 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Green, round, biconvex, prolonged-release tablets with a diameter of 8.6 – 9.0 mm and a height of 5.0 – 5.6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe pain, which can be adequately managed only with opioid analgesics.
Celastymis is indicated in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

The dosage depends on the intensity of pain and the patient's individual susceptibility to the treatment. The following general dosage recommendations apply:

Adults and adolescents 12 years of age and older
Dose titration and adjustment
In general, the initial dose for opioid naïve patients is 10 mg oxycodone hydrochloride given at intervals of 12 hours. Some patients may benefit from a starting dose of 5 mg oxycodone hydrochloride to minimize the incidence of adverse reactions.
Patients already receiving opioids may start treatment with higher dosages taking into account their experience with former opioid therapies.
For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

Generally, the lowest effective dose for analgesia should be selected. Increasing severity of pain will require an increased dosage of *Celastymis* tablets, using the different tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary, increases should be made in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of *Celastymis* tablets should be increased.

Because of individual differences in sensitivity for different opioids, it is recommended that patients should start conservatively with Celastymis after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

Celastymis is not intended for use as a prn analgesic.

Some patients who take Celastymis following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Celastymis is not indicated for the treatment of acute pain and/or breakthrough pain. The single dose of the rescue medication should amount to 1/6 of the equianalgesic daily dose of Celastymis. Use of the rescue medication more than twice daily indicates that the dose of Celastymis needs to be increased. The dose should not be adjusted more
often than once every 1-2 days until a stable twice daily administration has been achieved.

Following a dose increase from 10 mg to 20 mg taken every 12 hours dose adjustments should be made in steps of approximately one third of the daily dose. The aim is a patient-specific dosage which, with twice daily administration, allows for adequate analgesia with tolerable undesirable effects and as little rescue medication as possible as long as pain therapy is needed.

Even distribution (the same dose mornings and evenings) following a fixed schedule (every 12 hours) is appropriate for the majority of the patients. For some patients it may be advantageous to distribute the doses unevenly. In general, the lowest effective analgesic dose should be chosen. For the treatment of non-malignant pain a daily dose of 40 mg is generally sufficient; but higher dosages may be necessary. Patients with cancer-related pain may require dosages of 80 to 120 mg, which in individual cases can be increased to up to 400 mg. If even higher doses are required, the dose should be decided individually balancing efficacy with the tolerance and risk of undesirable effects. Doses in excess of 1000mg have been recorded.

Conversion from oral morphine
According to well-controlled clinical studies 10-13 mg oxycodone hydrochloride correspond to approximately 20 mg morphine sulphate, both in the prolonged-release formulation.
It must be emphasised that this is a guide to the dose of **Celastymis** tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Transferring patients between oral and parenteral oxycodone:
The dose should be based on the following ratio: 2 mg of oral oxycodone is equivalent to 1 mg of parenteral oxycodone. It must be emphasised that this is a guide to the dose required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients
Elderly patients without clinical manifestation of impaired liver and/or kidney function usually do not require dose adjustments.

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that, compared with younger adults, the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Patients with low body weight or slow metabolism
Risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially half the recommended adult dose if they are opioid naïve. Therefore the lowest recommended dosage, i.e. 10 mg, may not be suitable as a starting dose. Dose titration should be performed in accordance with the individual clinical situation.

Patients with renal or hepatic impairment
The dose initiation should follow a conservative approach as the plasma concentration may be increased in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

Use in non-malignant pain:
Opioids are not first line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. Types of chronic pain which have been shown to be alleviated by strong opioids include chronic osteoarthritic pain and intervertebral disc disease.

Children under 12 years of age
Oxycodone has not been studied in children younger than 12 years of age. The safety and efficacy of Celastymis have not been demonstrated and the use in children younger than 12 years of age is therefore not recommended.

Method of administration
For oral use.
Celastymis should be taken twice daily based on a fixed schedule at the dosage determined. The prolonged-release tablets may be taken with or independent of meals with a sufficient amount of liquid. Celastymis must be swallowed whole, not chewed, divided or crushed. Taking chewed, divided or crushed Celastymis tablets may lead to a rapid release and absorption of a potentially fatal dose of oxycodone.

Celastymis should not be taken with alcoholic beverages.

Treatment goals and discontinuation

Before initiating treatment with Celastymis, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient,
in accordance with pain management guidelines. During treatment, there should be frequent contact
between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with
oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In
absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
Celastymis should not be taken longer than necessary.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe respiratory depression with hypoxia and/or elevated carbon dioxide levels in the blood (hypercapnia).
- Severe chronic obstructive pulmonary disease.
- Cor pulmonale.
- Severe bronchial asthma.
- Paralytic ileus.
- Acute abdomen,
- Delayed gastric emptying.
- Head injury.
- Moderate to severe hepatic impairment.
- Severe renal impairment (creatinine clearance <10 ml/min).
- Chronic constipation.
- Concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use.
- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

"Do not use for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI)".

Caution must be exercised when administering oxycodone to the debilitated elderly, patients with severely impaired pulmonary function, patients with impaired hepatic or renal function, patients with myxoedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, intracranial lesions, head injury (due to risk of increased intracranial pressure), reduced level of consciousness of uncertain origin, sleep apnoea or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors (see section 4.5).

Respiratory and cardiac depression
Respiratory depression is the most significant risk induced by opioids and is most likely to occur in elderly or debilitated patients. The respiratory depressant effect of oxycodone can lead to increased carbon dioxide concentrations in blood and hence in cerebrospinal fluid. In predisposed patients opioids can cause severe decrease in blood pressure.

Oxycodone 60mg, 80mg and 120mg tablets should not be used in patients not previously exposed to opioids. These tablet strengths may cause fatal respiratory depression when administered to opioid naïve patients.

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone.

Repeated use of Celastymis may lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Celastymis may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).
Before initiating treatment with Celastymis and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained online, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction

The clinical need for analgesic treatment should be reviewed regularly.

Tolerance and dependence

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with oxycodone.
Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

For appropriate patients who suffer with chronic non-malignant pain, opioids should be used as part of a comprehensive treatment programme involving other medications and treatment modalities. A crucial part of the assessment of a patient with chronic non-malignant pain is the patient's addiction and substance abuse history.

If opioid treatment is considered appropriate for the patient, then the main aim of treatment is not to minimise the dose of opioid but rather to achieve a dose which provides adequate pain relief with a minimum of side effects.

Long-term use of Celastymis can cause the development of tolerance which leads to the use of higher doses in order to achieve the desired analgesic effect. There is a cross-tolerance to other opioids. Chronic use of Celastymis can cause physical dependence. Withdrawal symptoms may occur following abrupt discontinuation of therapy.

If therapy with oxycodone is no longer required it may be advisable to reduce the daily dose gradually in order to avoid the occurrence of a withdrawal syndrome.

Withdrawal symptoms may include restlessness, perspiration, chills, myalgia, palpitations, yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions and insomnia. Other symptoms also may develop, including: irritability, backache, joint pain, weakness, abdominal cramps, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate or heart rate.

If women take this drug during pregnancy there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Hepatobiliary disorders
Oxycodone may cause dysfunction and spasm of the Sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis. Therefore, oxycodone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.
Celastymis tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed, or crushed **Celastymis** tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9).
Concomitant use of alcohol and **Celastymis** may increase the undesirable effects of **Celastymis**; concomitant use should be avoided.
Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.
Empty matrix (tablets) may be seen in the stools. Opioids such as oxycodone hydrochloride may influence the hypothalamicpituitary- adrenal or – gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone.
Clinical symptoms may manifest from these hormonal changes.

Celastymis has a primary dependence potential. In patients with a history of alcohol and drug abuse the medicinal product must be prescribed with special care.

Abuse

Abuse of oral dosage forms by parenteral administration can be expected to result in other serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

Alcohol
Concomitant use of alcohol and Celastymis may increase the undesirable effects of Celastymis; concomitant use should be avoided.

Special patient groups
Caution is required in elderly or debilitated patients, in patients with severe impairment of lung, hepatic or renal function, myxoedema, hypothyroidism, Addison's disease (adrenal insufficiency), intoxic psychosis (e.g. alcohol), prostatic hypertrophy, adrenocortical insufficiency, alcoholism, known opioid dependence, delirium tremens, pancreatitis, disease of the biliary tract, biliary or renalcolic, inflammatory bowel disorders, raised intracranial pressure, hypotension, hypovolemia, epilepsy or seizure tendency and in patients taking MAO inhibitors within the last two weeks. Patients with severe hepatic impairment should be closely monitored.

Oxycodone should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, oxycodone should be discontinued immediately.

Surgical procedures
Special care should be taken when oxycodone is applied to patients undergoing bowel-surgery as opioids are known to impair intestinal motility. Opioids should only be administered post-operatively when the bowel function has been restored.

The safety of Celastymis used pre-operatively has not been established.

As with all opioid preparations, oxycodone products should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function.

Celastymis is not recommended for pre-operative use or within the first 12 – 24 hours post operatively.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive oxycodone tablets for 12 hours prior to the intervention.
If further treatment with oxycodone tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage. Opioids may also cause worsening of preexistingcentral sleep apnoea (see section 4.8).

Paediatric population
The safety and efficacy of Celastymis in children younger than 12 years of age have not been established. Celastymis should not be used in children younger than 12 years of age because of safety and efficacy concerns.

As with other opioids, infants who are born to dependent mothers may exhibit withdrawal symptoms and may have respiratory depression at birth.

Anti-doping warning
Athletes must be aware that this medicine may cause a positive reaction to 'antidoping' tests.

Use of Celastymis as a doping agent may become a health hazard.

To avoid damage to the controlled release properties of the tablets the prolonged release tablets must be swallowed whole, not chewed, divided or crushed. The administration of chewed, divided or crushed prolonged-release tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of oxycodone and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Oxycodone concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Endocrine system
Opioids may influence the hypothalamic-pituitary-adrenal or – gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Excipient
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Medicinal products affecting the central nervous system (CNS) include nonbenzodiazepine-containing sedatives, hypnotics, antipsychotics, antidepressants, antihistamines, antiemetics and other opioids.

Alcohol may enhance the pharmacodynamics effects of Celastymis; concomitant use should be avoided.

Concomitant administration of oxycodone, with serotonin agents, such as a Selective Serotonin Re uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

Anticholinergic drugs (e.g. psychotropic drugs, tricyclic antidepressants, antihistamines, antiemetics, muscle relaxants, Parkinson's disease drugs) may increase anticholinergic side effects of Oxycodone, such as constipation, dry mouth, or difficulty urinating.

Oxycodone should be used with caution in patients who have used or received MAO inhibitors in the last two weeks.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). Co-administration with monoamine oxidase inhibitors or within twso weeks of discontinuation of their use should be avoided.

Alcohol may enhance the pharmacodynamic effects of Celastymis; concomitant use should be avoided.

Clinically relevant changes in International Normalised Ratio (INR) in both directions have been observed in individuals if coumarin anticoagulants are co-applied with oxycodone.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6.
The activities of these metabolic pathways may be inhibited or induced by various co administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azole antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly.
Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 - 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 - 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St John´s Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.
Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

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

4.6 Pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.

Pregnancy

Oxycodone is not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone. If opioid use is required for a prolonged period in pregnant women, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone should, therefore, not be used in breastfeeding mothers.

Fertility
No human data on the effect of oxycodone on fertility are available. In rats there was no effect on mating or fertility with oxycodone treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines. This is particularly likely at the initiation of treatment with Celastymis, after dose increase or product rotation and if Celastymis is combined with other CNS depressant agents.

Patients stabilised on a specific dose will not necessarily be restricted. Therefore, the physician should decide whether the patient is allowed to drive or use machinery.
This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:
• The medicine is likely to affect your ability to drive.
• Do not drive until you know how the medicine affects you.
• It is an offence to drive while you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').
• This defence applies when:
    - The medicine has been prescribed to treat a medical or dental problem; And
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine.
• Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected)."

4.8 Undesirable effects

Summary of the safety profile

Due to its pharmacological properties oxycodone may cause respiratory depression, miosis, bronchial spasm and spasm of unstriated muscles and may suppress the cough reflex.

The most frequently reported undesirable effects are nausea (especially at the beginning of treatment) and constipation.

Respiratory depression is the chief hazard of an opioid overdose and occurs most commonly in elderly or debilitated patients.

The following frequency categories form the basis for classification of the undesirable effects:
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)

Infections and infestations

Rare:	Herpes simplex

Immune system disorders

Uncommon:	Hypersensitivity
Not known:	Anaphylactic responses, anaphylactoid reaction

Metabolism and nutrition disorders

Common:	Decreased appetite up to loss of appetite
Uncommon:	Dehydration
Rare:	Increased appetite

Psychiatric disorders

Common:	Anxiety, confusional state, depression, decreased activity, restlessness, psychomotor hyperactivity, nervousness, insomnia, abnormal thinking, abnormal dreams
Uncommon:	Agitation, affect lability, euphoric mood, perception disturbances (e.g. hallucinations, derealisation), decreased libido, drug dependence (see section 4.4)
Not known:	Aggression, drug dependence

Nervous system disorders

Very common:	Somnolence, sedation, dizziness, headache
Common:	Tremor, lethargy
Uncommon:	Amnesia, convulsion (especially in persons with epileptic disorder or predisposition to convulsions), concentration impaired, migraine, hypertonia, involuntary muscle contractions, hypoaesthesia, abnormal coordination, speech disorder, syncope, paraesthesia, dysgeusia
Not known:	Hyperalgesia

Eye disorders

Uncommon:	Visual impairment, miosis,

Ear and labyrinth disorders

Uncommon:	Hearing impaired, vertigo

Cardiac disorders

Uncommon:	Tachycardia, Palpitations (in the context of withdrawal syndrome), supraventricular tachycardia.

Vascular disorders

Uncommon:	Vasodilatation, facial flushing.
Rare:	Hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Common:	Dyspnoea, bronchospasm, cough decreased.
Uncommon:	Respiratory depression, dysphonia, cough

Gastrointestinal disorders

Very common:	Constipation, vomiting, nausea
Common:	Abdominal pain, diarrhoea, dry mouth, hiccups, dyspepsia
Uncommon:	Mouth ulceration, stomatitis, dysphagia, flatulence, eructation, ileus
Rare:	Melaena, tooth disorder, gingival bleeding
Not known:	Dental caries

Hepatobiliary disorders

Uncommon:	Increased hepatic enzymes, biliary colic
Not known:	Cholestasis, biliary colic, Sphincter of Oddi dysfunction

Skin and subcutaneous tissue disorders

Very common:	Pruritus
Common:	Skin reaction/rash, hyperhidrosis
Uncommon:	Dry skin
Rare:	Urticaria

Renal and urinary disorders

Common:	Dysuria, micturition urgency
Uncommon:	Urinary retention

Reproductive system and breast disorders

Uncommon:	Erectile dysfunction, hypogonadism
Frequency unknown:	Amenorrhoea

General disorders and administration site conditions

Common:	Asthenia, fatigue
Uncommon:	Chills, drug withdrawal syndrome, pain (e.g. chest pain), malaise, oedema, peripheral oedema, drug tolerance, thirst
Rare:	Weight increase, weight decrease
Not known:	Drug withdrawal syndrome neonatal

Injury, poisoning and procedural complications

Uncommon:	Injuries from accidents

Description of selected adverse reactions

Opioid Tolerance and Opioid Withdrawal Syndrome

The frequency of opioid tolerance and the frequency of opioid withdrawal syndrome cannot be estimated from available evidence (e.g. clinical trials, spontaneous reporting, and the medical literature) and therefore is classified as “not known” (see section 4.8). ‘Not known’ should not be interpreted as an indication of the rarity of the occurrence of opioid tolerance and opioid withdrawal syndrome, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency.

Drug dependence

The frequency above regarding drug dependence reflects the current evidence, including cumulative data from clinical trials and additional post marketing sources, and indicates that the risk of drug dependence with opioids is highly variable depending upon: definition of drug dependence; duration of treatment; dose; individual patient risk factors; and clinical settings. ‘Not known’ should not be interpreted as an indication of the rarity of the occurrence of drug dependence, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency.

Repeated use of Celastymis can lead to drug dependence, even at therapeutic doses. The risk of

drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of
opioid treatment (see section 4.4).

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 the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms of intoxication
Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing up to stupor or coma, hypotonia, miosis, bradycardia, hypotension, pulmonary oedema and death. Toxic leukoencephalopathy has been observed with oxycodone overdose.

Therapy of intoxication
A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

Opioid antagonists: Naloxone (e.g. 0.4-2 mg naloxone intravenously). Administration should be repeated at 2-3 minute intervals as necessary, or by an infusion of 2 mg naloxone in 500 ml 0.9% w/v sodium chloride solution or 5% w/v glucose solution (corresponding to 0.004 mg naloxone/ml).
If repeated doses are required an infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event that IV access is not possible. As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients.
For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.
The patient should be observed for at least 6 hours after the last dose of naloxone.
Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdosage.
Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may recipitate pain and an acute withdrawal syndrome.

The infusion should be run at a rate related to the previously administered bolus doses and should be in accordance with the patient's response.

Other supportive measures: These include artificial ventilation, oxygen, vasopressors, and fluid infusions in the management of circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Fluid and electrolyte balance should be maintained.

- Consider activated charcoal (50 g for adults, 10-15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however, there is no evidence to

support this.

- Celastymis tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and the management of oxycodone overdosage should be modified accordingly. Gastric contents may therefore need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; Opioids; Natural opium alkaloids
ATC-Code: N02A A05
Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain and spinal cord. It acts at these receptors as an opioid agonist without an antagonistic effect. The therapeutic effect is mainly analgesic, anxiolytic, antitussiveand sedative. Compared to rapid-release oxycodone, given alone or in combination with other substances, the prolonged-release tablets provide pain relief for a markedly longer period without increased occurrence of undesirable effects.

Gastrointestinal System
Opioids may induce spasm of the sphincter of Oddi.

Other pharmacological effects
In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown.
Whether oxycodone, a semi-synthetic opioid, has immunological effects similar to morphinie is unkown.

Clinical studies
The efficacy of oxycodone tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of oxycodone tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

5.2 Pharmacokinetic properties

Absorption:
The relative bioavailability of Celastymis is comparable to that of rapid release oxycodone with maximum plasma concentrations being achieved after approximately 3 hours after intake of the prolonged-release tablets compared to 1 to 1.5 hours. Peak plasma concentrations and oscillations of the concentrations of oxycodone from the prolonged-release and rapid-release formulations are comparable when given at the same daily dose at intervals of 12 and 6 hours, respectively.

The tablets must not be crushed, divided, or chewed as this leads to rapid oxycodone release and absorption of a potentially fatal dose of oxycodone due to the damage of the prolonged release properties.

Distribution:
The absolute bioavailability of oxycodone is approximately two thirds relative to parenteral administration. In *steady state*, the volume of distribution of oxycodone amounts to 2.6 l/kg; plasma protein binding to 38-45%; the elimination half-life to 4 to 6 hours and plasma clearance to 0.8 l/min. The elimination half-life of oxycodone from prolonged-release tablets is 4-5 hours with steady state values being achieved after a mean of 1 day.

Metabolism:
Oxycodone is metabolized in the intestine and liver via the (CYP3A4 and CYP2D6) P450 cytochrome system to noroxycodone and oxymorphone as well as to several glucuronide conjugates. In vitro studies suggest that therapeutic doses of cimetidine probably have no relevant effect on the formation of noroxycodone. Noroxycodone is a weak mu opioid agonist. Noroxymorphone is a potent mu opioid agonist; however, it does not cross the blood-brain barrier to a significant extent. Oxymorphone is a potent mu opioid agonist but is present at very low concentrations following oxycodone administration. In man, quinidine reduces the production of oxymorphone while the pharmacodynamic properties of oxycodone remain largely unaffected. The contribution of the metabolites to the overall pharmacodynamic effect is irrelevant.

Elimination:
Oxycodone and its metabolites are excreted via urine and faeces. Oxycodone crosses, the placenta and is found in breast milk. The mean apparent elimination half-life of Celastymis is 4.5 hours, which leads to steady-state being achieved in about one day. The active drug and its metabolites are excreted in urine.

Linearity/non-linearity:
Across the 5-80 mg dose range of prolonged release oxycodone tablets linearity of plasma concentrations was demonstrated in terms of rate and extent of absorption.

Elderly
The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender
Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment
Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in t½ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment
Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone

peak plasma concentrations and AUC values were lower by 15% to 50%. The t½ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Reproductive and developmental toxicity Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual foetuses were analyzed.

However, when the same data were analyzed using litters as opposed to individual foetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/d group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the foetal findings may have been a secondary consequence of severe maternal toxicity.

In a study of peri- and postnatal development in rats, maternal body weight and food intake parameters were reduced for doses ≥ 2 mg/kg/d compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/d dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/d based on body weight effects seen at 6 mg/kg/d). There were no effects on the F2 generation at any dose in the study.

Carcinogenicity
Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.
Carcinogenicity was evaluated in a 2-year oral gavage study conducted in Sprague-Dawley rats. Oxycodone did not increase the incidence of tumours in male and female rats at doses up to 6 mg/kg/day. The doses were limited by opioid-related pharmacological effects of oxycodone.

Mutagenicity
The results of in-vitro and in-vivo studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

Oxycodone was not genotoxic in a bacterial mutagenicity assay or in an in-vivo micronucleus assay in the mouse. Oxycodone produced a positive response in the invitro mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 μg/mL. Two in-vitro chromosomal aberrations assays with human lymphocytes were conducted. In the first assay, oxycodone was negative without metabolic activation but was positive with S9 metabolic activation at the 24 hour time point but not at other time points or at 48 hour after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Ammonio Methacrylate Copolymer, Type B dispersion 30%
Povidone (K29/32)
Talc

Triacetin
Stearyl alcohol
Magnesium stearate

Tablet coating:
Hypromellose
Macrogol 400
Titanium dioxide (E171)
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172)

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

Child resistant PVC/PVdC-Aluminium blisters with 10, 14, 20, 25, 28, 30, 40, 50, 56, 60, 98 and 100 prolonged-release tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novumgen Limited
20-22 Wenlock Road,
London, N1 7GU,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 55863/0069

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 2023

10 DATE OF REVISION OF THE TEXT

06/05/2025