janssen

JURNISTA®
Prolonged-release Tablets

DATA SHEET

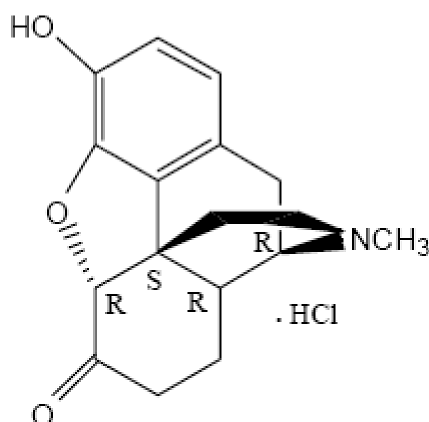
NAME OF THE DRUG

Hydromorphone hydrochloride

DESCRIPTION

Hydromorphone hydrochloride has four asymmetric carbon atoms (C_5, C_9, C_{13} and C_{14}), with a specific rotation (20°C, 589 nm) of –136.5° to –138.5°. No cis-trans isomerism or threo-erythro isomerism was detected. No other isomers are known.

Hydromorphone hydrochloride has the following structural formula:



4,5α-epoxy-3-hydroxy-17-methyl-morphinan-6-one hydrochloride

CAS: 71-68-1 $C_{17}H_{19}NO_3$.HCl MW: 321.8

Hydromorphone hydrochloride is freely soluble in water, very slightly soluble in ethanol and practically insoluble in methylene chloride.

JURNISTA tablets have been formulated using the OROS® osmotic pump (push-pull) bilayer tablet with a semi-permeable cellulose acetate coating that controls the rate at which water is absorbed into the tablet after it has been swallowed. A laser-drilled hole on the drug side of the tablet allows the dissolved/suspended drug to be released from the tablet at a controlled rate as it passes through the gastrointestinal tract.

The JURNISTA tablet is non-deformable and does not appreciably change in shape in the GI tract; patients should be advised not to be alarmed if they notice what appears to be the JURNISTA tablet in their stools, as it is simply the non-dissolvable shell.

JURNISTA is available as prolonged-release tablets containing 4, 8, 16, 32 and 64 mg hydromorphone hydrochloride.

JURNISTA tablets contain the inactive ingredients:

Coated tablet core: polyethylene oxide, povidone, magnesium stearate, butylated hydroxytoluene (E321), polyethylene oxide, sodium chloride, hypromellose, iron oxide black (E172), lactose anhydrous, cellulose acetate, macrogol 3350 and iron oxide yellow (E172) (for the 32 mg strength only)

Colour overcoat: lactose monohydrate, hypromellose, titanium dioxide (E171), glycerol triacetate and iron oxide red (E172) (for the 8 mg strength)/iron oxide yellow (for the 16 mg strength)/indigo carmine lake (E132) (for the 64 mg strength).

Clear overcoat: hypromellose and macrogol 400.

Printing ink: iron oxide black (E172), propylene glycol and hypromellose.

PHARMACOLOGY

Hydromorphone is principally an agonist of μ-receptors, showing a weak affinity for κ- and δ-receptors. Analgesia occurs as a consequence of the binding of hydromorphone to the μ-receptors of the CNS.

Pharmacodynamics

As with all opioid analgesics, hydromorphone exerts its principal pharmacological effects on the CNS and smooth muscle, including the gastrointestinal tract, by binding to specific opioid receptors.

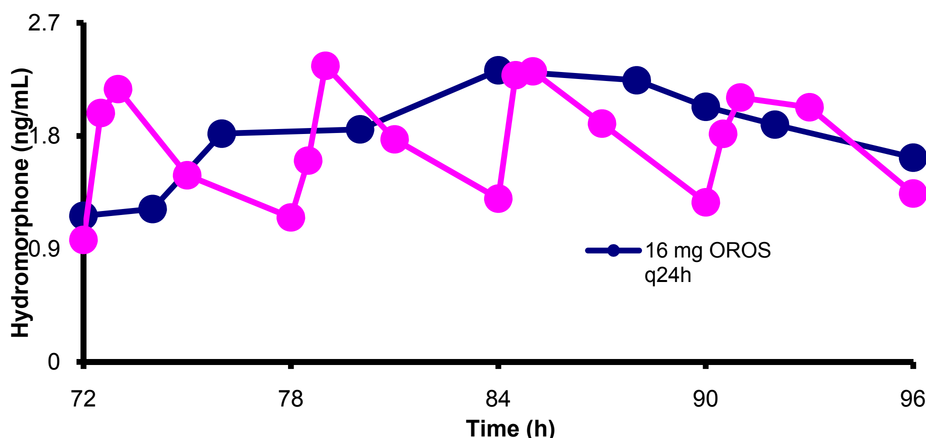
Although estimates vary (from 2 to 10 times), oral hydromorphone appears to be approximately 5 times as potent (by weight) as morphine and has a shorter duration of effect. Opioid analgesics cause respiratory depression principally by direct action on cerebral respiratory control centres. Opioids inhibit gastrointestinal motility. Opioids may cause nausea and vomiting due to direct stimulation of the chemoreceptors for emesis in the posterior area of the medulla, cause euphoria, sedation, mood changes and pupil constriction, and suppress cough reflex.

Pharmacokinetics

Following oral dosing of JURNISTA prolonged-release tablets, plasma concentrations reach a broad, relatively plateau region within 6 to 8 hours and remain in this plateau region until approximately 24 hours post-dose; the mean T_{max} values were approximately 13 to 16 hours. This demonstrates that, as intended, hydromorphone is released in a controlled manner from the dosage form, with drug absorption continuing throughout the intestinal tract for approximately 24 hours, consistent with once-daily dosing. The mean absolute bioavailability from JURNISTA ranged from 22% to 26%. The concomitant administration of JURNISTA with a high fat meal has no effect on the absorption of hydromorphone.

Steady state plasma concentrations are approximately twice those observed following the first dose, and steady state is reached by the fourth dose of JURNISTA. No time-dependent change in pharmacokinetics was seen with multiple dosing. At steady state, JURNISTA given once daily maintained hydromorphone plasma concentrations within the same concentration range as the immediate-release tablet given 4 times daily at the same total daily dose and diminishes the periodic fluctuations in plasma levels seen with the immediate-release tablet. The degree of fluctuation in plasma concentration at steady state during a 24-hour period [*(calculated as* $(C_{max(ss)} – C_{min(ss)}/C_{avg(ss)})$ *x 100%)*] was lower with JURNISTA (83%) as compared to the overall fluctuations of the immediate-release tablet (147%) (see Figure 1). At steady state, hydromorphone AUC for JURNISTA is equivalent to that observed for the immediate-release tablet.

Figure 1. Steady-State Plasma Concentration Profile (n = 18 naltrexone blocked healthy subjects)



Plasma protein binding is low (< 30%). Glucuronidation is the main metabolic pathway and the principal metabolite is the inactive hydromorphone 3-glucuronide, which follows a similar time course to hydromorphone in plasma. Unlike morphine, no active 6-glucuronide metabolite is produced. Linear pharmacokinetics has been demonstrated for the prolonged-release tablet over the dose range 8 to 64 mg, with dose proportional increases in plasma concentrations (C_{max}) and overall exposure (AUC).

The effect of age on the pharmacokinetics of hydromorphone immediate-release resulted in a 14% decrease in C_{max} and a modest increase (11%) in AUC in the elderly compared to the young. No difference in T_{max} was observed. These effects are considered unlikely to be clinically relevant. Greater sensitivity of older individuals cannot be excluded. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

Hydromorphone plasma concentrations and pharmacokinetic parameters following administration of JURNISTA are comparable in male and female subjects.

In studies that used oral dosing with conventional tablets, hepatic impairment reduces the first-pass metabolism of hydromorphone such that four-fold higher plasma levels of hydromorphone are seen in subjects with moderate hepatic dysfunction. Renal impairment affected the pharmacokinetics of hydromorphone and its metabolite, hydromorphone 3-glucuronide, following administration of an immediate-release tablet. The effects of renal impairment on hydromorphone pharmacokinetics were two-fold and four-fold increases in hydromorphone bioavailability in moderate and severe renal impairment, respectively. There were also substantial changes in hydromorphone 3-glucuronide elimination kinetics for the severe renal impairment group, although haemodialysis was effective at reducing plasma levels of both hydromorphone and metabolites. (see **DOSAGE AND ADMINISTRATION**).

In a study evaluating hydromorphone absorption from JURNISTA when taken with 240 mL of 4%, 20% and 40% alcohol, C_{max} increased on average by 17, 31, and 28% respectively in the fasting state and was less affected in the fed state with increases of 14, 14, and 10% respectively. Median T_{max} (fasted and fed) with 4, 20 and 40% alcohol was 12 to 16 hour and with no alcohol was 16 hour. No effect was seen on AUC values both in the fed and fasted state. Concomitant use of alcohol should be avoided (see **PRECAUTIONS**).

Clinical studies

The JURNISTA clinical development program included 4 controlled safety and efficacy studies: DO-118, DO-119, DO-132, and M03-644.

The four controlled studies were conducted in patients with cancer pain (Study DO-118), patients with osteoarthritis (OA) pain (Studies DO-132 and M03-644), and patients with non-malignant or cancer pain (Study DO-119). Three of the four controlled studies evaluated JURNISTA against an active control: morphine sulfate SR (DO-118), OxyContin® (DO-132), and IR hydromorphone (DO-119). Study M03-644 was placebo-controlled.
The three active-controlled studies included a titration phase where patients had their dose of JURNISTA adjusted to obtain the optimum balance of benefits and side effects. In Study M03-644, patients were assigned a fixed dose of JURNISTA and no dose adjustments were allowed.

Study demographics and trial design for the four controlled studies are presented below.

Study Demographics and Trial Design

Table 1: Summary of Patient Demographics for JURNISTA Clinical Trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
M03-644	Double-blind, fixed-dose, parallel-group, placebo-controlled study	Oral administration of JURNISTA 8 mg, 16 mg, or placebo qd with 12 wks double-blind treatment period	n = 981 (319 for 8 mg, 330 for 16 mg, 332 for placebo)	59 y (22, 89)	354 M 627 F
DO-118	Double-blind, ascending-dose, parallel-group, active-controlled study	Oral administration of immediate-release (IR) hydromorphone and morphine sustained-release (SR) morphine and JURNISTA, IR phase: 2-9 d, SR phase: 10-15 d	IR phase: n = 200 (99 for hydromorphone, 101 for morphine) SR phase: n = 163 (77 for JURNISTA, 86 for morphine SR)	IR phase: 60.5 y (19, 82) SR phase: 60 y (27, 81)	98 M, 102 F 82 M 81 F
DO-119	Randomized, double-blind, 3-arm parallel study	Oral administration of JURNISTA and immediate-release hydromorphone to hydromorphone-tolerant patients. Titration phase: 14 d, randomized treatment: 7 d	n = 113 (39 for immediate-release HM, 74 for JURNISTA)	44 y (27, 81)	57 M 56 F
DO-132	Open-label, dose titration, 2-arm parallel study	Oral administration of JURNISTA q.d. or OxyContin b.i.d. Titrate to best balance between pain relief and tolerability (14 d) followed by maintenance phase of 28 d	n = 138 (71 for JURNISTA, 67 for OxyContin)	65 y (39, 91)	44 M 94 F

Study Results

The primary objective for DO-118, conducted in patients with cancer pain who received and/or required strong opioid analgesics, was to demonstrate the clinical equivalence of hydromorphone and a standard opioid analgesic, morphine (in both immediate-release [IR] and sustained-release [SR] formulations), using the "worst pain" item of the Brief Pain Inventory (BPI). The equivalence between the two treatments was defined by a 95% 2-sided confidence interval (CI) for the difference between the adjusted mean values for the 2 treatments at phase endpoint of –1.5 to +1.5. Equivalence was demonstrated for the IR treatment phase with a 95% CI for treatment difference of (–0.4, 0.9). The 95% CI for the SR phase was (–1.59, –0.01); the result was outside the confidence band and favoured

JURNISTA. The findings indicate that the hydromorphone and morphine IR and SR treatments were equivalent. Other than Brief Pain Inventory rating for morning (AM) and evening (PM) in the SR phase, where patients treated with JURNISTA had a lower pain intensity PM mean adjusted score (2.6) than patients treated with morphine SR (3.4), p=0.0372, no statistically significant differences were observed in any other secondary efficacy measures, such as the use of breakthrough pain medication.

Study DO-132 was a multicentre, open-label, randomized, repeated-dose, 2-arm, parallel-group study characterizing the efficacy and safety of JURNISTA once daily and extended-release oxycodone b.i.d. in patients with chronic osteoarthritis (OA) of the knee and hip who were on chronic non-steroidal anti-inflammatory drug (NSAID) or other non-steroidal, non-opioid analgesic (i.e., acetaminophen or aspirin) therapy. Efficacy results from the two primary efficacy endpoints in this study, mean pain relief scores at endpoint and mean number of treatment days to moderate to complete pain relief, demonstrated the similarity between JURNISTA and extended-release oxycodone. No treatment-related differences were observed for the results of the other efficacy measurements except for two items on the MOS Sleep Problems Index I: significantly less sleep disruption and daytime drowsiness at the last assessment (p=0.0114) and less sleep disruption between baseline and the last assessment (evidenced by the change from baseline; p=0.0448), both favouring JURNISTA over extended- release oxycodone.

DO-119 was a multicentre, randomized, double-blind, repeated-dose, parallel-group study designed to compare the efficacy and tolerability of JURNISTA and immediate-release hydromorphone in patients with chronic pain. The primary efficacy variable was change in total daily dose of breakthrough pain medication, IR hydromorphone, supported by the frequency of breakthrough medication use. JURNISTA and IR hydromorphone treatment groups both had significant increases from baseline (end of titration phase) to endpoint (end of double-blind phase) in total daily dose of rescue medication (all p values were < 0.027) demonstrating equivalence between JURNISTA and IR hydromorphone. In addition, there was a numerically small and not statistically significant difference (p=0.760) for changes in rescue medication use between JURNISTA (+2.0 mg) and IR hydromorphone (+4.4 mg). Similarly, the median change in the number of times per day that rescue medication was used from baseline to endpoint was +0.25 for the group treated with JURNISTA, and +0.40 for the IR hydromorphone treatment group, and was not statistically significant (p=0.743).

INDICATIONS

JURNISTA is indicated in the treatment of moderate to severe chronic pain.

CONTRAINDICATIONS

JURNISTA is contraindicated in:

- Patients with a known hypersensitivity to hydromorphone or to any of the tablet excipients.
- Patients who have had surgical procedures and/or underlying disease that would result in narrowing of the gastrointestinal tract, or have “blind loops” of the gastrointestinal tract or gastrointestinal obstruction.
- The management of acute post-operative pain.
- Patients with status asthmaticus.
- Children, or women during pregnancy, labour, and delivery

PRECAUTIONS

Opioid analgesics, including hydromorphone, may cause severe hypotension in an individual whose ability to maintain blood pressure is compromised by a depleted blood volume or concomitant administration of drugs such as phenothiazines or general anaesthetics.

If during treatment, paralytic ileus is suspected, the treatment should be stopped. JURNISTA should not be used in situations with risk of paralytic ileus.

In the case of chordotomy or other pain-relieving operations, patients should not be treated with JURNISTA within 24 hours after the operation. After an effective pain-relieving procedure, re-titration of oral opioid requirements using IR preparations is recommended. JURNISTA should not be administered within 18 hours prior to such procedures.

Impaired respiration

Respiratory depression is the most important hazard of opioid preparations but occurs most frequently in overdose situations, in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate doses may dangerously decrease respiration. JURNISTA, like all other opioids, should be used with extreme caution in patients with a substantially decreased respiratory reserve or pre-existing respiratory depression and in patients with chronic obstructive pulmonary disease. Severe pain antagonises the respiratory depressant effects of opioids. However, should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for regional anaesthetic procedures or other interruptions of pain transmission pathways should not receive JURNISTA within 24 hours of the procedure but should be provided with immediate release opioid analgesics. Concomitant administration of hydromorphone with other opioid analgesics is associated with an increased risk of respiratory failure. Therefore, it is important to reduce the dose of hydromorphone when other analgesics are given concomitantly.

Head injury and increased intracranial pressure

The respiratory depressant effects of opioids with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury or raised intracranial pressure. Opioids produce effects that may obscure neurological signs of further increases in intracranial pressure in patients with head injuries. JURNISTA should only be administered under such circumstances when considered essential and then with extreme caution.

Gastrointestinal tract and other smooth muscle

Like other opioids, hydromorphone causes a reduction in gastrointestinal motility associated with an increase in smooth muscle tone. Consequently, constipation is a frequent side effect reported with treatment with opioids. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in patients with chronic constipation.

Clinical conditions or medicinal products that cause a sudden and significant shortening of gastrointestinal transit time may result in decreased hydromorphone absorption with JURNISTA and may potentially lead to withdrawal symptoms in patients with a physical dependence on opioids.

The administration of opioids may obscure the diagnosis or clinical course of acute abdominal conditions. Therefore, it is important to make sure that the patient is not suffering from intestinal occlusion, especially of the ileus, before initiation of treatment. Hydromorphone also can cause an increase in biliary tract pressure as a result of spasm in the sphincter of Oddi. Caution should therefore be exercised in the administration of JURNISTA to patients with inflammatory or obstructive bowel disorders, acute pancreatitis secondary to biliary tract disease and in patients about to undergo biliary surgery.

The JURNISTA tablet is non-deformable and does not appreciably change in shape in the GI tract. There have been very rare reports of obstructive symptoms in patients with known strictures in association with ingestion of medicinal products in non-deformable controlled-release formulations (see **CONTRAINDICATIONS**).

Patients should be advised not to be alarmed if they notice what appears to be the JURNISTA tablet in their stools, as it is simply the non-dissolvable shell.

Carcinogenicity

Long-term carcinogenicity studies have not been performed. Hydromorphone is well established in clinical practice in several countries over a number of decades without any epidemiological indication of carcinogenicity in humans.

Genotoxicity

Hydromorphone was not genotoxic in bacterial reverse mutation assays or *in vivo* in mouse micronucleus assays. The genotoxic risk of hydromorphone in patients from the recommended clinical use is considered low.

Effects on fertility

In a fertility study in the rat, a slight but statistically significant reduction in implantations was observed at 6.25 mg/kg/day, a dose level that produced maternal toxicity. Male and female fertility were unaffected up to doses of 6.25 mg/Kg/day. A low incidence of testicular tubular atrophy was documented in a repeated dose study in rats at a dose of 14 mg/kg/day. The effects of JURNISTA on human fertility are unknown.

Use in pregnancy

Category C.

JURNISTA should not be used during pregnancy and labour due to impaired uterine contractility and the risk of respiratory depression in newborn infant. Withdrawal symptoms may be observed in the newborn of mothers undergoing chronic treatment.

Hydromorphone crosses the placental barrier in experimental animals. No significant effects on embryofetal development were observed in rats during foetal organogenesis at maternal doses of hydromorphone up to 3.13 mg/kg/day. No teratogenicity was seen in the rat up to doses of 6.25 mg/kg/day. Maternal toxicity was observed in rabbits at doses of 12.5 mg/kg/day and higher, however, there were no signs of embryotoxicity or tetratogenicity in the rabbit fetuses at doses up to 25 mg/kg/day.

Use in lactation

No clinical data are available on the use of hydromorphone during lactation. Low concentrations of hydromorphone and other opioid analgesics have been detected in human milk in clinical studies. Preclinical studies have shown that following a single dose of [14C] hydromorhone to lactating rats, less than 1% of radiolabelled material was secreted into milk in 24 hours after dosing. Neonatal viability and development were also adversely affected in rats at maternal doses of 3.13 mg/kg and higher. JURNISTA should not be used during breast-feeding.

Use in children

The safety and efficacy of JURNISTA in children and adolescents under the age of 18 has not been established. Until further experience is gained, JURNISTA must not be used in this population.

Use in the elderly

Elderly people are more prone to CNS adverse effects (confusion) and gastrointestinal disturbances, and physiological reduction of renal function. Therefore, extra caution should be shown, and the initial dose should be reduced. Concomitant use of other medications, especially tricyclic antidepressants, increases the risk of confusion and constipation. Diseases in the prostate gland and the urinary tract are often seen in the elderly; this contributes to the increased risk of urinary retention. The above considerations should emphasize the importance of caution rather than imply a restriction of the use of opioids in the elderly.

Use in patients with hepatic and renal impairment

Moderate and severe renal impairment results in two-fold and four-fold increases in hydromorphone bioavailability respectively. Moderate hepatic impairment results in a four-fold increase in hydromorphone plasma levels. Patients with moderate hepatic or renal insufficiency should be started on a reduced dose and closely monitored during dose titration. In patients with severe renal insufficiency an increased dosing interval should also be considered and these patients should, in addition, be monitored during maintenance therapy for development of opioid-related adverse reactions. (see **DOSAGE AND ADMINISTRATION**)

Use in special risk patients

JURNISTA, like all opioid analgesics, should be administered with caution and in reduced dosages in patients with moderate to severe renal or hepatic insufficiency, adrenocortical insufficiency, myxoedema, hypothyroidism, prostatic hypertrophy or urethral stricture. Caution should also be exercised in the administration of JURNISTA to patients with CNS depression, kyphoscoliosis, toxic psychosis, acute alcoholism, delirium tremens, or convulsive disorders.

Drug dependence

With the continued use of opioids, including JURNISTA, the development of tolerance and physical dependence may be expected. Physical dependence is a state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued.

JURNISTA should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of opioid tolerance and psychological dependence observed in these patient populations. . Intravenous administration of some non-active components of JURNISTA to animals has been shown to cause anemia, degeneration and necrosis of myocardial cells and renal tubular epithelial cells and death. With abuse by parenteral routes, the tablet excipients may cause lethal complications. **JURNISTA must not be administered by a parenteral route.** Oral use of these excipients was not associated with negative findings.

The deliberate abuse of JURNISTA may occur, as happens with other opioids, and is characterized by changes in behaviours, which are not seen in patients whose pain is treated appropriately with JURNISTA. The development of psychological dependence or an addictive effect is believed to occur only in individuals who may be predisposed in some way and is not a normal or expected response to the appropriate administration of opioids for pain management. However, even if a patient has misused opioids in the past, hydromorphone or other opioids could still be indicated in the treatment of severe pain in the patient. In most cases the request reflects a real need for pain relief and should not be mistaken for inappropriate use of the medicinal product. Since alcohol increases the sedative effect of hydromorphone concomitant use of JURNISTA and alcohol should be avoided.

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

Effects of ability to drive and use machinery

JURNISTA can have a major influence on the ability to drive and use machines. This is particularly likely at the start of therapy, following an increase in dose or change of preparation.

Interactions with other drugs

Monoamine oxidase inhibitors (MAOIs) may cause CNS excitation or depression, hypotension or hypertension if co-administered with opioids. JURNISTA is not intended for patients taking MAOIs or within 14 days of stopping such treatment.

The concomitant use of hydromorphone with morphine agonist/antagonists such as buprenorphine, nalbuphine or pentazocine, could lead to a reduction of the analgesic effect by competitive blocking of receptors, thus leading to risk of withdrawal symptoms. Therefore, this combination is not recommended.

The concomitant use of other central nervous system depressants such as hypnotics, sedatives, general anaesthetics, antipsychotics and alcohol may cause additive depressant effects, and respiratory depression. Additionally, hypotension and profound sedation or coma may occur. Therefore, when this combination is indicated, the dose of one or both agents should be reduced.

JURNISTA, like other opioids, may enhance the neuromuscular blocking action of muscle relaxants and cause an increased degree of respiratory depression.

The concomitant use of alcohol should be avoided. Alcohol increases the sedative effect of hydromorphone (see Pharmacokinetics). In addition, peak hydromorphone concentrations are increased when JURNISTA is taken with alcohol (mean 30-35%). Due to the OROS® technology in JURNISTA, the prolonged-release properties of JURNISTA are maintained in the presence of alcohol.

ADVERSE REACTIONS

Clinical Studies Data

The safety of JURNISTA was evaluated by pooling safety data from 12 studies: 4 controlled and 8 uncontrolled, open-label safety and efficacy studies. The total number of patients who received JURNISTA in those studies was 1684 patients.

The four controlled studies were conducted in patients with cancer, osteoarthritis and non-malignant or cancer pain. Three of the four controlled studies evaluated JURNISTA against an active control: morphine sulphate sustained-release, oxycodone controlled-release and hydromorphone immediate-release; the fourth study was placebo-controlled.

The eight uncontrolled studies were conducted in patients with cancer pain, non-cancer pain, lower back pain, chronic pain or acute pain. The most common adverse reactions related to JURNISTA were the opioid-related GI events of constipation, nausea and vomiting, and opioid-related nervous system events of somnolence, headache and dizziness.

Respiratory depression may be more likely in certain subgroups of patients (see **PRECAUTIONS**).

The following adverse drug reactions (ADRs) were reported in the above-mentioned clinical trials:

Very Common (≥ 1/10)

Nervous system disorders:	Somnolence, headache, dizziness
Gastrointestinal disorders:	Constipation, nausea, vomiting
General disorders & administration site conditions:	Asthenia

Common (≥ 1/100 to < 1/10)

Metabolism & nutrition disorders:	Anorexia, dehydration
Psychiatric disorders:	Insomnia, anxiety, confusional state, nervousness, nightmares, depression, mood swings, restlessness, hallucination
Nervous system disorders:	Memory impairment, hypoaesthesia, paraesthesia, tremor or involuntary muscle contractions, sedation, disturbance in attention, dysgeusia

Eye disorders: Visual disorders such as blurred vision

Ear & labyrinth disorders: Vertigo

Cardiac disorders: Tachycardia

Vascular disorders: Hypotension, flushing, hypertension

Respiratory, thoracic & mediastinal disorders: Dyspnoea

Gastrointestinal disorders: Dry mouth, diarrhoea, abdominal pain, dyspepsia, dysphagia, flatulence

Skin & subcutaneous tissue disorders: Hyperhidrosis, pruritus, rash

Musculoskeletal & connective tissue disorders: Muscle spasms, back pain, arthralgia, pain in extremity

Renal & urinary disorders: Urinary retention, dysuria, micturition urgency

General disorders & administration site conditions: Oedema, drug withdrawal syndrome, pyrexia, pain, chest discomfort, chills

Investigations: Weight decreased

Injury, poisoning & procedural complications: Fall, contusion

Uncommon (≥ 1/1000 to < 1/100)

Infections & infestations: Gastroenteritis, diverticulitis

Metabolism & nutrition disorders: Increased appetite, fluid retention, hyperuricaemia

Psychiatric disorders: Libido decreased, panic attack, paranoia, aggression, crying, listless, dysphoria, euphoric mood

Nervous system disorders: Myoclonus, coordination abnormal, dyskinesia, syncope, dysarthria, balance disorder, depressed level of consciousness, hyperaesthesia, encephalopathy, cognitive disorder, psychomotor hyperactivity, fits/convulsions

Eye disorders: Miosis, diplopia, dry eye

Ear & labyrinth disorders: Tinnitus

Cardiac disorders: Palpitations, extrasystoles

Respiratory, thoracic & Mediastinal disorders: Respiratory distress, rhinorrhoea, hypoxia, bronchospasm, hyperventilation, sneezing

Gastrointestinal disorders: Abdominal distension, haemorrhoids, haematochezia, abnormal faeces, intestinal obstruction, diverticulum, eructation, gastrointestinal motility disorder, large intestine perforation

Musculoskeletal & connective tissue disorders: Myalgia

Renal & urinary disorders: Urinary hesitation, pollakiuria

Reproductive system & breast Disorders: Erectile dysfunction/impotence, sexual dysfunction

General disorders & administration site conditions: Feeling abnormal, malaise, difficulty in walking, feeling jittery, hangover

Investigations: Oxygen saturation decreased, blood potassium decreased, hepatic enzyme increased, blood amylase increase

Injury, poisoning & procedural
Complications: Overdose

Rare (≥ 1/10,000 to <1/1000)

Endocrine disorders: Hypogonadism

Nervous system disorders: Hyperreflexia

Cardiac disorders: Bradycardia

Respiratory, thoracic &
Mediastinal disorders: Respiratory depression

Gastrointestinal disorders: Anal fissure, bezoar, duodenitis, ileus, impaired gastric emptying, painful defaecation

Hepatobiliary disorders: Biliary colic

Skin & subcutaneous
tissue disorders: Reddening of face/erythema

General disorders & administration
site conditions: Feeling drunk, feeling hot and cold, hypothermia

Investigations: Blood testosterone decreased

DOSAGE AND ADMINISTRATION

As with other opioid analgesics, safe and effective administration of JURNISTA to patients with pain depends upon a comprehensive assessment of the patient. The nature of the pain as well as the concurrent medical status of the patient will affect selection of the dose. Owing to the varied response observed to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose of opioid therapy and titrated to an adequate level of analgesia, balanced against an acceptable frequency of adverse reactions.

As with any strong opioid, appropriate prophylaxis for known adverse reactions (for example constipation), should be considered.

Patients should be instructed to swallow JURNISTA tablet whole with a glass of water, at approximately the same time each day, and never to chew, divide, or crush it.

JURNISTA should not be taken more than once every 24 hours.

If the patient did not take the regularly scheduled dose of JURNISTA, the patient should be instructed to take the next dose immediately and start a new 24-hour regimen.

Opioid-naïve patients (currently not routinely receiving opioids)

It is recommended to begin treatment with conventional immediate-release preparations (e.g. immediate-release hydromorphone or immediate-release morphine) and then convert to the appropriate total daily dose of JURNISTA, because it may be more time consuming to titrate a patient to adequate analgesia using a controlled release opioid preparation. For conversion, please refer to the conversion table below. If a decision is being made to initiate patients on JURNISTA, the starting dose of JURNISTA should not exceed 8 mg every 24 hours. Some patients may benefit from an initial titration dose of 4 mg every 24 hours to improve tolerability. The dose may be titrated upwards, if required, in increments of either 4 or 8 mg depending on response and supplementary analgesic requirements. Dose should not be titrated more frequently than every 2 days.

Opioid-tolerant patients (currently receiving opioids regularly)

In patients currently taking opioid analgesics, the starting dose of JURNISTA should be based on the prior daily opioid dose (the total opioid daily dose in milligrams regardless of the dosage form), using standard equi-analgesic ratios. For opioids other than morphine, first estimate the equivalent total daily dose of morphine, then use the conversion table below (Table 2) to determine the equivalent total daily dose of JURNISTA.

Table 2: Conversion Table: Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of JURNISTA

(mg/day Prior Opioid x Factor = mg/day JURNISTA)

Prior Opioid	**Oral Prior Opioid (factor)**	**Parenteral Prior Opioid (factor)**
Morphine	0.2	0.6
Hydromorphone	1	4

No fixed conversion ratio is likely to be satisfactory in all patients, due to individual patient and formulation differences. Therefore, patients should be converted to the recommended starting dose of JURNISTA followed by close monitoring and titration if required.

Dosages should be rounded down to the closest dose of JURNISTA available in 4 mg increments (4, 8, 16, 32 and 64 mg tablets), as clinically indicated.

All other around-the-clock opioid analgesic medications should be discontinued when JURNISTA therapy is initiated.

JURNISTA can also be safely used with usual doses of non-opioid analgesics and analgesic adjuvants.

Supplemental Rescue Medication

In addition to once-daily JURNISTA therapy, supplemental breakthrough pain medication in the form of immediate release preparations (e.g., immediate release hydromorphone or immediate release morphine) could be made available to all patients with chronic pain. For conversion, the conversion table should be used. Individual supplemental doses of immediate release hydromorphone or immediate release morphine should generally not exceed 10% to 25% of the 24 hour JURNISTA dose (see Table 3 below).

Table 3: Recommended Starting Dose for Supplemental Rescue Medication

Daily JURNISTA Dosage (mg)	**Immediate Release hydromorphone Tablet Strength (mg) per Dose**	**Immediate Release morphine (mg)**
8	2	10
16	2	10-15
32	4	20-30
64	8	40-60

Individualization of dosage and maintenance of therapy:

After initiation of therapy with JURNISTA, dose adjustments may be necessary to obtain the patient's best balance between pain relief and opioid-related adverse reactions.

If the pain increases in severity or analgesia is inadequate, a gradual increase in dosage may be required. In order to allow the effects of the dose change to stabilise, the dosage should be increased no more frequently than every two days. As a guideline, dosage increases of 25%-100% of the current daily dose of JURNISTA should be considered for each titration step.

Once patients become stable on once-daily JURNISTA therapy, the dose may be continued for as long as pain relief is necessary. The continued need for around-the-clock opioid therapy and adjustments in therapy should be reassessed periodically as appropriate.

Use in children and adolescents

JURNISTA is not recommended for use in children and adolescents below the age of 18 due to insufficient data on safety and efficacy.

Use in the elderly

The medical setting of the elderly is often complex. Therefore, treatment with JURNISTA should be initiated cautiously at a reduced initial dose.

Use in patients with renal and hepatic impairment

Following administration of hydromorphone immediate-release tablets, the following results were observed in clinical studies:

- In patients with moderate hepatic insufficiency (scoring 7-9 on Child-Pugh rating scale) both exposure (plasma AUC) and peak plasma concentrations of hydromorphone were approximately 4-times higher compared with healthy controls and the elimination half-life was unaltered.
- In patients with moderate renal insufficiency (creatinine clearance of 40-60 mL/min), exposure (plasma AUC) to hydromorphone were approximately 2-times higher than in those with normal renal function and the elimination half-life was unaltered.
- In patients with severe renal insufficiency (creatinine clearance < 30 mL/min), exposure (plasma AUC) to hydromorphone was approximately 4-times greater than in those with normal renal function and the elimination half-life was 3-times longer.

Therefore, patients with moderate hepatic or renal insufficiency should be started on a reduced dose and be closely monitored during dose titration. In patients with severe renal insufficiency an increased dosing interval should also be considered and these patients should, in addition, be monitored during maintenance therapy for development of opioid-related adverse reactions.

Discontinuation of therapy

In patients who are physically dependent on opioids and receiving daily administration of hydromorphone, abrupt discontinuation of treatment with JURNISTA will result in symptoms of withdrawal syndrome. Therefore, if discontinuation of therapy with JURNISTA is indicated in patients, the dose of JURNISTA should be reduced by 50% every 2 days until the lowest possible dose is reached, at which time therapy may be safely discontinued. If symptoms of withdrawal appear, tapering should be stopped. The dose should be slightly increased until the signs and symptoms of opioid withdrawal disappear. Tapering should then begin again but with longer periods of time between each JURNISTA dose reduction, or before converting to an equianalgesic dose of another opioid to continue tapering.

OVERDOSAGE

Opioid overdosage is characterized by respiratory depression, drowsiness, which progresses to stupor and coma, musculoskeletal flaccidity, cold skin, contracted pupils and, at times, tachycardia and hypotension. In cases of severe overdosage, apnoea, circulatory collapse, cardiac arrest and death may occur.

In the treatment of overdosage, primary attention should be given to the reestablishment of adequate respiratory exchange keeping the airway open and instituting assisted or controlled ventilation. If the oral ingestion was recent, gastric contents may be emptied by gastric lavage, as indicated.

Supportive measures (including oxygen and vasopressors) should be used to manage the shock and pulmonary oedema, which potentially accompany overdose. Cardiac arrest and arrhythmias may require cardiac massage or defibrillation.

In cases of severe overdosage, specific antidotes such as naloxone and nalmefene should be used to manage respiratory depression (see the prescribing information for the specific opioid antagonist for detail of proper use).

The effect of naloxone is relatively short; therefore, the patient should be carefully monitored until respiration has stabilised. JURNISTA will release hydromorphone for approximately 24 hours. This should be taken into account in determining the treatment. Opioid antagonists should not be given in the absence of clinically significant respiratory depression, or circulatory depression because of opioids. Opioid antagonists should be administered with caution to patients suspected to be physically dependent on hydromorphone, since rapid reversal of an opioid, including hydromorphone, may precipitate symptoms of withdrawal.

PRESENTATION

All strengths of JURNISTA tablets are available in blister packs of 7, 10, 14, 20, 28, 30, 35, 40, 50, 60 and 100 tablets.

- JURNISTA 4 mg tablets are pale beige, round, biconvex with 'HM 4' printed in black ink on one side.
- JURNISTA 8 mg tablets are red, round, biconvex with 'HM 8' printed in black ink on one side.
- JURNISTA 16 mg tablets are yellow, round, biconvex with 'HM 16' printed in black ink on one side.
- JURNISTA 32 mg tablets are white, round, biconvex with 'HM 32' printed in black ink on one side.
- JURNISTA 64 mg tablets are blue, round, biconvex with 'HM 64' printed in black ink on one side.

JURNISTA 4, 8, 16, 32 and 64mg tablets are not currently marketed in New Zealand.

Storage

JURNISTA tablets should be kept out of reach of children. Store at or below 25 °C.

MEDICINE CLASSIFICATION

Controlled Drug – B3.

SPONSOR

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NEW ZEALAND

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