

## PRODUCT MONOGRAPH

<sup>N</sup>**JURNISTA**<sup>®\*</sup>

hydromorphone hydrochloride Prolonged Release Tablets  
4, 8, 16, and 32 mg

Opioid Analgesic

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**Table of Contents**

PART I: HEALTH PROFESSIONAL INFORMATION..... 3

    SUMMARY PRODUCT INFORMATION ..... 3

    INDICATIONS AND CLINICAL USE..... 3

    CONTRAINDICATIONS ..... 4

    WARNINGS AND PRECAUTIONS..... 4

    ADVERSE REACTIONS..... 10

    DRUG INTERACTIONS ..... 16

    DOSAGE AND ADMINISTRATION ..... 18

    OVERDOSAGE ..... 21

    ACTION AND CLINICAL PHARMACOLOGY ..... 22

    STORAGE AND STABILITY ..... 25

    SPECIAL HANDLING INSTRUCTIONS ..... 25

    DOSAGE FORMS, COMPOSITION AND PACKAGING ..... 25

PART II: SCIENTIFIC INFORMATION ..... 27

    PHARMACEUTICAL INFORMATION..... 27

    CLINICAL TRIALS ..... 28

    DETAILED PHARMACOLOGY ..... 31

    TOXICOLOGY ..... 31

    REFERENCES ..... 36

PART III: CONSUMER INFORMATION..... 38

# <sup>N</sup>JURNISTA<sup>®</sup>

hydromorphone hydrochloride

Prolonged-Release Tablets  
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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Prolonged-Release Tablet 4 mg, 8 mg, 16 mg, and 32 mg	butyl hydroxytoluene, cellulose acetate, glycerol triacetate, iron oxide black, ferric oxide red (8 mg only), ferric oxide yellow (16 mg and 32 mg only), hypromellose, lactose anhydrous, lactose monohydrate, macrogol, magnesium stearate, polyethylene oxide, povidone, propylene glycol, sodium chloride and titanium dioxide.  JURNISTA <sup>®</sup> may contain traces of sodium metabisulfite.

### INDICATIONS AND CLINICAL USE

#### Adults

JURNISTA<sup>®</sup> (hydromorphone hydrochloride) tablets are indicated for the management of moderate to severe chronic pain in adults who require continuous around-the-clock opioid analgesia.

#### Geriatrics (> 65 years of age)

The elderly are more prone to central nervous system (CNS) adverse effects, gastrointestinal disturbances and physiological reduction of renal function. Caution is advised during initiation and maintenance treatment, especially if there are concomitant medications (see **DOSAGE AND ADMINISTRATION**).

## **Pediatrics (< 18 years of age)**

The use of JURNISTA<sup>®</sup> in children under 18 years of age is not recommended, as dosage requirements for the safe and efficacious use of JURNISTA<sup>®</sup> have not been established for this patient population.

## **CONTRAINDICATIONS**

JURNISTA<sup>®</sup> (hydromorphone hydrochloride) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing of excipients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Patients who have had surgical procedures and/or underlying disease that may result in narrowing of the gastrointestinal tract, or have “blind loops” of the gastrointestinal tract or gastrointestinal obstruction.
- Patients who have ileus of any type.
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild, intermittent or short duration pain that can otherwise be managed.
- The management of acute pain.
- The management of perioperative pain.
- Patients with acute asthma or other obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women during pregnancy, labour and delivery.

## **WARNINGS AND PRECAUTIONS**

### **General**

**JURNISTA<sup>®</sup> (hydromorphone hydrochloride) tablets must be swallowed whole. JURNISTA<sup>®</sup> tablets should never be chewed, divided, or crushed. Taking broken or divided JURNISTA<sup>®</sup> could lead to the uncontrolled release and rapid absorption of a potentially fatal dose of hydromorphone.**

**Tablet strengths of 16 mg or higher are only for opioid tolerant patients requiring hydromorphone equivalent dosages of 16 mg or higher per day. These doses may lead to severe medical consequences, including fatal respiratory depression, in patients not previously exposed to similar daily doses of opioids at the time of switching to JURNISTA<sup>®</sup>. JURNISTA<sup>®</sup> is for continuous opioid coverage, given once a day in patients who require treatment for several days or more. Because it may be more time consuming to titrate a patient**

not routinely taking opioids to adequate analgesia using a controlled-release opioid preparation, it is advisable to have patients titrated to a satisfactory level of pain relief with an immediate-release opioid prior to conversion to the appropriate total daily dose of JURNISTA<sup>®</sup>.

Patients who have received JURNISTA<sup>®</sup> should be closely monitored, especially for signs of respiratory depression, until a stable maintenance dose is reached. Since alcohol increases the sedative effect of opioids, the concomitant use of JURNISTA<sup>®</sup> and alcohol should be avoided.

## **Gastrointestinal**

### **Potential for Gastrointestinal Obstruction**

Because the JURNISTA<sup>®</sup> tablet is non-deformable and does not appreciably change in shape in the gastrointestinal (GI) tract, JURNISTA<sup>®</sup> should not be administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel’s diverticulum) or in patients with dysphagia or significant difficulty in swallowing tablets.

There have been very rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of medicinal products in non-deformable controlled-release formulations (see **ADVERSE REACTIONS**).

### **Constipation**

JURNISTA<sup>®</sup> causes a reduction in gastrointestinal motility associated with an increase in smooth muscle tone. Constipation is a frequent side effect reported with opioid treatment. 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.

### **Gastrointestinal Transition**

Clinical conditions or medical products that cause a sudden and significant shortening of gastrointestinal transit time may result in decreased hydromorphone absorption from JURNISTA<sup>®</sup> and may potentially lead to withdrawal symptoms in patients with a physical dependence on opioids. Appropriate coverage with an immediate-release opioid formulation should be considered.

Due to the controlled-release design, JURNISTA<sup>®</sup> tablets should only be used in patients who are able to swallow the tablets whole. The JURNISTA<sup>®</sup> tablet is non-deformable and does not appreciably change in shape in the GI tract. Patients should be advised that the depleted JURNISTA<sup>®</sup> shells are excreted in their stool in the original shape.

### **Acute Abdominal Conditions**

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, including ileus, before initiation of treatment.

## **Abuse and Diversion**

JURNISTA<sup>®</sup> tablets are intended for oral use only. Abuse can lead to overdose and even death. This risk is increased when the tablet is crushed, broken, or chewed, and with concurrent consumption of alcohol or other CNS depressants. With abuse by parenteral route, the tablet contents may cause lethal complications.

Patients must be instructed NOT to give JURNISTA<sup>®</sup> to anyone else. Diversion will have serious medical consequences, including death.

## **Dependence/Tolerance**

JURNISTA<sup>®</sup> contains hydromorphone, a strong opioid. Tolerance and physical dependence tend to develop upon repeated administration of hydromorphone, and there is a potential for development of psychological dependence. However, tolerance as well as both physical and psychological dependence, are not by themselves evidence of an addictive disorder or abuse. Iatrogenic addiction following appropriate opioid administration for pain relief is relatively rare.

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, diarrhea, or increased blood pressure, respiratory rate, or heart rate. In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION, Cessation of Therapy**).

JURNISTA<sup>®</sup> 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.

With abuse by parenteral route, the tablet excipients may cause lethal complications (see **TOXICOLOGY**).

## **Cardiovascular**

**Hypotension:** Opioid analgesics, including hydromorphone, may cause severe hypotension in an individual whose ability to maintain blood pressure is compromised because of lower blood volume or concomitant administration of drugs such as phenothiazines or general anesthetics (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

## **Endocrine and Metabolism**

JURNISTA<sup>®</sup> should be administered with caution and in reduced dosages in patients with adrenocortical insufficiency, myxedema, and hypothyroidism.

## **Genitourinary**

JURNISTA<sup>®</sup>, like all opioid analgesics, should be administered with caution and in reduced dosages in patients with prostatic hypertrophy or urethral stricture.

## **Hepatic/Biliary/Pancreatic**

Patients with moderate hepatic insufficiency should be started on a reduced JURNISTA<sup>®</sup> dose and be closely monitored. If indicated, great caution and careful monitoring should be exercised for patients with severe hepatic insufficiency (see **DOSAGE AND ADMINISTRATION**).

Opioids 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<sup>®</sup> to patients with inflammatory or obstructive bowel disorders, or acute pancreatitis secondary to biliary tract disease, and in patients about to undergo biliary surgery.

## **Neurologic**

**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<sup>®</sup> should only be administered under such circumstances when it is considered essential and then with extreme caution, and is contraindicated in patients with increased cerebrospinal or intracranial pressure, and head injury (see **CONTRAINDICATIONS**).

## **Perioperative Considerations**

JURNISTA<sup>®</sup> is contraindicated for perioperative pain relief. In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with JURNISTA<sup>®</sup> within 24 hours before or after the operation. Thereafter, if JURNISTA<sup>®</sup> is to be continued after the patient recovers from the postoperative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated (see **DOSAGE AND ADMINISTRATION, Cessation of Therapy**).

The administration of analgesics in the perioperative period should be managed by health care providers with adequate training and experience (e.g., by an anesthesiologist).

## **Psychomotor Impairment**

Hydromorphone may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This is particularly likely at the start of therapy, following an increase in dose or change of preparation. Patients should be advised not to drive a car or operate machinery unless they are tolerant to the effects of JURNISTA<sup>®</sup>.

## **Renal**

Patients with moderate renal insufficiency should be started on a reduced JURNISTA<sup>®</sup> 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**).

## **Respiratory**

### **Respiratory Depression**

Respiratory depression is the most important hazard of opioid preparations. JURNISTA<sup>®</sup> should be used with extreme caution in patients having a substantially decreased respiratory reserve or pre-existing respiratory depression, and in patients with chronic obstructive pulmonary disease, hypoxia, or hypercapnia. Such patients are often less sensitive to the stimulatory effects of carbon dioxide (CO<sub>2</sub>) on the respiratory centre and the respiratory depressant effects of hydromorphone may reduce respiratory drive to the point of apnea.

Severe pain antagonizes the respiratory-depressant effects of opioids. However, should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for regional anesthetic procedures or other interruptions of pain transmission pathways should not receive JURNISTA<sup>®</sup> within 24 hours of the procedure. 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.

## **Sensitivity/Resistance**

### **Galactose Intolerance**

Lactose is a non-medicinal ingredient in JURNISTA<sup>®</sup>. Patients with rare hereditary diseases of galactose intolerance (galactosemia or glucose-galactose malabsorption) should not take this medicine.

### **Sulfite Allergy**

JURNISTA<sup>®</sup> may contain traces of sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

## **Patient Counseling Information**

A patient information sheet is included in the package of JURNISTA<sup>®</sup> tablets dispensed to the patient.

Patients receiving JURNISTA<sup>®</sup> should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including

children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.

2. Patients should be advised that JURNISTA<sup>®</sup> contains hydromorphone, an opioid pain medicine.
3. Patients should be advised that JURNISTA<sup>®</sup> should only be taken as directed. The dose of JURNISTA<sup>®</sup> should not be adjusted without consulting with a physician or other healthcare professional.
4. JURNISTA<sup>®</sup> should be swallowed whole (not crushed, divided, or chewed) due to a risk of fatal hydromorphone overdose.
5. Patients should not combine JURNISTA<sup>®</sup> with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur resulting in serious injury or death.
6. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with JURNISTA<sup>®</sup>.
7. Patients should be advised that if they have been receiving treatment with JURNISTA<sup>®</sup> and cessation of therapy is indicated, it may be appropriate to taper the JURNISTA<sup>®</sup> dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
8. Patients should be advised of the most common adverse reactions that may occur while taking JURNISTA<sup>®</sup>: constipation, nausea, vomiting, somnolence, headache and dizziness.
9. Patients should be advised that JURNISTA<sup>®</sup> may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on JURNISTA<sup>®</sup> or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of JURNISTA<sup>®</sup>.
10. As with other opioids, patients taking JURNISTA<sup>®</sup> should be advised of the potential for constipation; patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered.
11. Patients should be advised that JURNISTA<sup>®</sup> is a potential drug of abuse. They should protect it from theft or misuse.
12. Patients should be advised that JURNISTA<sup>®</sup> should never be given to anyone other than the individual for whom it was prescribed.
13. Patients should be advised that JURNISTA<sup>®</sup> 16 mg or higher is for use only in opioid-tolerant patients.

## **Special Populations**

**Pregnant Women:** JURNISTA<sup>®</sup> is contraindicated during pregnancy, labour and delivery due to impaired uterine contractility and the risk of neonatal respiratory depression. No clinical data on pregnant women exposed to JURNISTA<sup>®</sup> are available. While studies in rats and rabbits have revealed no teratogenic effects, reproductive toxicity has been observed. Hydromorphone has been shown to cross the placental barrier in experimental animals. The potential teratogenic risk for humans from the use of hydromorphone and other opiates during pregnancy is unknown. Withdrawal symptoms may be observed in the newborn of mothers undergoing chronic opioid treatment (see **CONTRAINDICATIONS**).

**Nursing Women:** Preclinical studies have shown that hydromorphone can be detected in the milk of lactating rats. Low concentrations of hydromorphone and other opioid analgesics have been detected in human milk in clinical studies. JURNISTA<sup>®</sup> should not be used during breast-feeding.

**Pediatrics (< 18 years of age):** The use of JURNISTA<sup>®</sup> in children under 18 years of age is not recommended, as dosage requirements for the safe and efficacious use of JURNISTA<sup>®</sup> have not been established for this patient population.

**Geriatrics (> 65 years of age):** The elderly are more prone to CNS adverse effects and gastrointestinal disturbances, and physiological reduction of the 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 of the prostate gland and the urinary tract are often seen in the elderly. This contributes to the increased risk of urinary retention.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The most common adverse reactions related to JURNISTA<sup>®</sup> were opioid-related gastrointestinal events of constipation, nausea, and vomiting, and opioid-related nervous system events of somnolence, headache, and dizziness.

The most serious adverse reaction associated with opioid therapy is respiratory depression. Use of an opioid dose that is higher than the opioid tolerance level of the patient may lead to fatal respiratory depression. Respiratory depression due to overexposure may be more likely in certain subgroups of patients, such as in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate doses may lead to fatal respiratory depression (see **WARNINGS AND PRECAUTIONS**).

## **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The safety of JURNISTA<sup>®</sup> was evaluated from the safety data of 13 studies in chronic pain. The 13 studies were conducted in patients with cancer pain and non-malignant pain, including osteoarthritis (OA) pain, and low back pain. In total, 2335 patients had received JURNISTA<sup>®</sup> for pain treatment.

### **Placebo-Controlled Studies**

The placebo-controlled safety database for JURNISTA<sup>®</sup> contains 268 patients with chronic low back pain, and 981 patients with osteoarthritis pain.

#### **Low Back Pain**

The study in chronic low back pain was a 12-week double-blind placebo-controlled, randomized withdrawal study with flexible dosing. A total of 447 patients were enrolled into the open-label titration phase with 268 patients randomized into the double-blind treatment phase. In the open-label phase, patients were converted to and titrated to a stable dose with JURNISTA<sup>®</sup>.

At the beginning of the double-blind phase, patients were randomized (in a 1:1 ratio) to either JURNISTA<sup>®</sup> or the matching placebo dosage, administered daily for up to 12 weeks. Patients who were randomized to placebo received JURNISTA<sup>®</sup> in dosages tapering from their stable Conversion and Titration phase dosage to placebo over a maximum of 14 days.

Overall discontinuation rates during the double-blind phase were 50.7% in JURNISTA<sup>®</sup>-treated patients and 67.2% in placebo-treated patients. There were no occurrences of gastrointestinal obstruction or respiratory depression.

The most common treatment-emergent adverse events ( $\geq 2\%$ ) reported during the titration phase were constipation, diarrhea, dry mouth, nausea, vomiting, drug withdrawal syndrome, fatigue, oedema peripheral, arthralgia, back pain, dizziness, headache, somnolence, anxiety, insomnia, hyperhidrosis and pruritis. Table 1.1 summarizes the treatment-emergent adverse events for JURNISTA<sup>®</sup> and placebo-treated patients from the placebo-controlled low back pain study.

**Table 1.1: Treatment-Emergent Adverse Events Reported in a JURNISTA<sup>®</sup> Chronic Pain Trial in patients with low back pain (≥1% and more frequent than the placebo group)**

	<i>JURNISTA<sup>®</sup></i> % (n = 134)	<i>Placebo</i> % (n = 134)
<b>Gastrointestinal disorders</b>		
Abdominal pain	1.5	0
Constipation	7.5	3.7
Dry mouth	1.5	0
Nausea	9.0	7.5
Toothache	2.2	0
Vomiting	6.0	4.5
<b>General disorders and administration site conditions</b>		
Irritability	1.5	0
Oedema Peripheral	2.2	0.7
Pyrexia	1.5	0.7
<b>Infections and infestations</b>		
Bronchitis	1.5	0
Gastroenteritis	1.5	0
Gastroenteritis viral	1.5	0.7
Influenza	3.0	1.5
Sinusitis	4.5	0.7
Upper respiratory tract infection	3.0	2.2
Urinary tract infections	3.0	1.5
<b>Investigations</b>		
Weight decreased	3.0	2.2
<b>Metabolism and nutrition disorders</b>		
Dehydration	1.5	0.7
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	6.0	2.2
Joint Swelling	1.5	0
Muscle Spasms	2.2	0.7
Pain in Extremity	1.5	0.7
<b>Nervous system disorders</b>		
Dizziness	2.2	1.5
Hypersomnia	1.5	0
<b>Psychiatric disorders</b>		
Insomnia	5.2	3.7
<b>Respiratory, thoracic and mediastinal disorders</b>		
Nasal Congestion	2.2	1.5
Oropharyngeal Pain	1.5	0
Respiratory Tract Congestion	1.5	0
Rhinorrhoea	1.5	0.7
<b>Vascular disorders</b>		
Hypotension	1.5	0

### Osteoarthritis Pain

In the placebo-controlled study with osteoarthritis pain, both opioid naïve and current opioid users were included. The current opioid users were receiving a daily morphine equivalent dose of < 40 mg. All patients were randomly assigned to placebo or a fixed dose of JURNISTA<sup>®</sup> (8 or 16 mg) with no dose adjustments allowed. Overall discontinuation rates were 43.7% (145/332 patients) from placebo treatment, 50.8% (162/319 patients) from the 8 mg treatment, and 61.2% (202/330 patients) from the 16 mg treatment. Adverse events were the predominant reason for discontinuation from active treatment and lack of analgesia was the predominant reason for discontinuation from placebo treatment. Adverse events that led to discontinuation of the active study medication were most frequently the common opioid-related events, constipation, nausea, somnolence, dizziness and headache. No deaths occurred during the study or within 30 days after completion of the study treatments. Table 1.2 summarizes the treatment-emergent adverse events for JURNISTA<sup>®</sup> and

placebo-treated patients from the placebo-controlled study in osteoarthritis pain.

**Table 1.2: Treatment-Emergent Adverse Events Reported in a JURNISTA<sup>®</sup> Chronic Pain Trial in patients with osteoarthritis pain (≥1% and more frequent than the placebo group)**

	<b>JURNISTA<sup>®</sup></b> <b>%</b> <b>(n = 649)</b>	<b>Placebo</b> <b>%</b> <b>(n = 332)</b>
<b>Cardiac disorders</b>		
Palpitations	1.1	0
<b>Ear and labyrinth disorders</b>		
Vertigo	1.5	0.6
<b>Gastrointestinal disorders</b>		
Constipation	44.1	11.7
Nausea	33.3	9.6
Vomiting	10.3	2.1
Dry mouth	5.7	2.7
Dyspepsia	2.2	1.5
Abdominal pain	3.5	1.5
Flatulence	1.5	1.2
<b>General disorders and administration site conditions</b>		
Fatigue	8.0	2.4
Oedema	2.2	1.8
Pyrexia	1.1	0
<b>Infections and infestations</b>		
Influenza	2.8	2.4
Gastroenteritis viral	2.3	0.9
Urinary tract infections	1.5	0.6
Viral infection	1.5	0.3
<b>Injury, poisoning and procedural complications</b>		
Contusion	1.1	0.9
<b>Investigations</b>		
Weight decreased	1.4	0.3
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	2.5	0.6
Anorexia	1.8	0.3
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	2.9	2.1
<b>Nervous system disorders</b>		
Headache	12.9	11.4
Somnolence	15.7	4.8
Dizziness	12.6	6.0
Lethargy	1.7	0
Paraesthesia	1.1	0.9
Tremor	1.2	0.6
<b>Psychiatric disorders</b>		
Insomnia	4.8	3.3
Anxiety	2.6	0.9
Depression	1.5	0.3
Irritability	1.1	0.3
Libido decreased	1.2	0
<b>Respiratory, thoracic and Mediastinal disorders</b>		
Pharyngolaryngeal pain	1.8	0.6
Dyspnoea	1.4	0.6
<b>Skin and subcutaneous tissue disorders</b>		
Pruritus	11.2	2.4
Hyperhidrosis	2.8	0
Rash	2.0	0.6
<b>Vascular disorders</b>		
Hot flush	1.1	0

## All Clinical Studies

The following treatment-emergent adverse reactions were identified premarketing based on pooling the safety data from the 13 studies. Of the 2335 patients who had received JURNISTA<sup>®</sup>, 420 patients were treated with JURNISTA<sup>®</sup> for at least 6 months, while 141 patients were treated with JURNISTA<sup>®</sup> for more than 12 months.

A total of 64 deaths were reported in the 13 studies during or after JURNISTA<sup>®</sup> treatment. Fifty-eight deaths were attributed to cancer and six were associated with other conditions (cardiac arrest in two patients and sepsis, respiratory failure/dehydration, myocardial infarction, and congestive heart failure, each in one patient). All of the deaths were considered unrelated or unlikely related to drug treatment.

Respiratory depression was reported in one patient with cancer pain. The event, which occurred on day 263 of JURNISTA<sup>®</sup> treatment, was considered mild in intensity and definitely related to drug treatment but did not require cessation of JURNISTA<sup>®</sup> treatment. Six gastrointestinal obstructive events were reported: small intestinal obstruction in two patients; and intestinal obstruction, fecaloma, bezoar, and gastric outlet obstruction, each in one patient. All events occurred in the context of predisposing conditions (i.e., pathologic or iatrogenic gastrointestinal narrowing, Crohn's disease, colon cancer, colon resection, colon tortuosity, previous bowel obstruction, gall bladder surgery, gastric ulcer, vagotomy, antrectomy, pyloroplasty, and chronic constipation with chronic laxative abuse). For the bezoar and fecaloma events, there was no evidence of OROS<sup>®</sup> shells in the impacted material.

The most common treatment-emergent adverse reactions related to JURNISTA<sup>®</sup> were opioid-related gastrointestinal events of constipation, nausea, and vomiting, and opioid-related nervous system events of somnolence, headache, and dizziness. The safety profile for JURNISTA<sup>®</sup> is consistent with those of other strong opioids.

### Clinical Trial Treatment-Emergent Adverse Reactions

Following are the treatment-emergent adverse reactions from the 13 JURNISTA<sup>®</sup> studies in patients with chronic pain:

**Table 1.3: Treatment-Emergent Adverse Reactions**

System Organ Class	Treatment-Emergent Adverse Reaction			
	Frequency			
	Very Common (≥10%)	Common (≥1% to <10%)	Uncommon (≥0.1% to 1%)	Rare (≥ 0.01% to 0. 1%)
<b>Cardiac disorders</b>		tachycardia	palpitations, extrasystoles	bradycardia
<b>Ear and labyrinth disorders</b>		vertigo	tinnitus	
<b>Endocrine disorders</b>				hypogonadism
<b>Eye disorders</b>		vision blurred	diplopia, dry eye	miosis
<b>Gastrointestinal disorders</b>	constipation, nausea, vomiting	diarrhea, abdominal pain, dry mouth, dyspepsia, dysphagia, flatulence	haematochezia, abdominal distension, haemorrhoids, abnormal faeces, intestinal obstruction, diverticulum,	anal fissure, bezoar, duodenitis, ileus, impaired gastric emptying, painful defaecation

System Organ Class	Treatment-Emergent Adverse Reaction			
	Frequency			
	Very Common (≥10%)	Common (≥1% to <10%)	Uncommon (≥0.1% to 1%)	Rare (≥ 0.01% to 0. 1%)
			eructation, gastrointestinal motility disorder, large intestine perforation	
<b>General disorders and administration site conditions</b>	Asthenia	edema, pyrexia, pain, chest discomfort, chills, drug withdrawal syndrome	malaise, feeling abnormal, feeling jittery, difficulty in walking, hangover	feeling drunk, feeling hot and cold, hypothermia
<b>Infections and infestations</b>			gastroenteritis, diverticulitis	
<b>Injury, poisoning and procedural complications</b>		fall, contusion	overdose	
<b>Investigations</b>		weight decreased	oxygen saturation decreased, blood potassium decreased, hepatic enzyme increased, blood amylase increased	blood testosterone decreased
<b>Metabolism and nutrition disorders</b>		anorexia, dehydration	fluid retention, increased appetite, hyperuricaemia	
<b>Musculoskeletal and connective tissue disorders</b>		muscle spasms, back pain, arthralgia, pain in extremity	myalgia	
<b>Nervous system disorders</b>	somnolence, headache, dizziness	hypoesthesia paraesthesia, tremor, sedation, memory impairment, disturbance in attention, dysgeusia	dysarthria, syncope, balance disorder, coordination abnormal, depressed level of consciousness, hyperaesthesia, dyskinesia, myoclonus, encephalopathy, cognitive disorder, psychomotor hyperactivity, fits/convulsions	hyperreflexia
<b>Psychiatric disorders</b>		insomnia, anxiety, depression, confusional state, nervousness, abnormal dreams, restlessness, hallucination, mood altered	libido decreased, panic attack, euphoric mood, listless, paranoia, aggression, crying, suicide ideation	dysphoria
<b>Renal and urinary disorders</b>		dysuria, urinary retention	pollakiuria, urinary hesitation, micturition disorder	

System Organ Class	Treatment-Emergent Adverse Reaction			
	Frequency			
	Very Common (≥10%)	Common (≥1% to <10%)	Uncommon (≥0.1% to 1%)	Rare (≥ 0.01% to 0. 1%)
<b>Reproductive system and breast disorders</b>			erectile dysfunction, sexual dysfunction	
<b>Respiratory, thoracic and mediastinal disorders</b>		dyspnea	rhinorrhoea, hypoxia, respiratory distress, bronchospasm, hyperventilation, sneezing	respiratory depression
<b>Skin and subcutaneous tissue disorders</b>		pruritus, hyperhidrosis, rash	erythema	
<b>Vascular disorders</b>		flushing, hypertension	Hypotension	

## DRUG INTERACTIONS

### Overview

The low level of protein binding of hydromorphone to human plasma proteins (less than 30%) makes it unlikely to result in protein-displacement drug-drug interactions.

*In vitro* and *in vivo* data suggest that hydromorphone in clinical practice has minimal potential to moderate the activity of human hepatic CYP450 activities. Metabolism of hydromorphone is predominantly through conjugation with glucuronic acid as a first-pass effect, with no identified active metabolites and with little potential for drug-drug interactions at the level of metabolizing enzymes.

CNS depressants, such as other opioids, anesthetics, sedatives, hypnotics, barbiturates, phenothiazines, chloral hydrate and glutethimide may enhance the depressant effects of hydromorphone. MAO inhibitors (including procarbazine HCl) should not be taken within two weeks of use. Pyrazolidone antihistamines, beta-blockers and alcohol may also enhance the depressant effects of hydromorphone. When combined therapy is contemplated, the dose of one or both agents should be reduced.

### Drug-Drug Interactions

#### **CNS Depressants**

CNS depressants, such as other opioids, general anesthetics, sedatives, hypnotics, barbiturates, phenothiazines, other antipsychotics, and glutethimide may enhance the depressant effects of hydromorphone. The concomitant use of central nervous system depressants may cause additive depressant effects and respiratory depression. Additionally, hypotension and profound sedation or coma may occur. Pyrazolidone antihistamines, beta-blockers and alcohol may also enhance the depressant effects of hydromorphone. When this combination therapy is indicated with these drugs, the dose of one or both agents should be reduced.

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

The concomitant use of alcohol should be avoided. Alcohol increases the sedative effect of hydromorphone.

### **Monoamine oxidase inhibitors**

Monoamine oxidase inhibitors (MAOIs) may cause CNS excitation or depression, hypotension or hypertension if co-administered with opioids. JURNISTA<sup>®</sup> is contraindicated in patients taking MAOIs or within 14 days of stopping such treatment. MAO inhibitors (including procarbazine) should not be taken within two weeks of using JURNISTA<sup>®</sup>.

### **Mixed agonist-antagonist opioid analgesics**

The concomitant use of hydromorphone (a pure opioid agonist) with mixed agonist-antagonist opioid analgesics (buprenorphine, nalbuphine, pentazocine) could lead to a reduction of the analgesic effect by competitive blocking of receptors, thus leading to a risk of withdrawal symptoms. Therefore, this combination is not recommended.

### **Alcohol Interaction Studies**

In vitro dissolution studies have demonstrated no dose dumping with JURNISTA<sup>®</sup> in the presence of 4, 20, or 40% alcohol (% v/v) with continuous exposure to alcohol over 24 hours.

The effect of co-administering 240 ml 4-40% alcohol on the pharmacokinetics of hydromorphone from a 16 mg JURNISTA<sup>®</sup> tablet was evaluated in healthy subjects. The maximum concentration of hydromorphone ( $C_{max}$ ) increased on average between 10 to 31% with the co-administration of alcohol. Median  $T_{max}$  values were similar across treatment groups and there were no effects seen in AUC values (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Co-administration of 240 mL 4%, 20% and 40% alcohol (% v/v) increased  $C_{max}$  on average by 17%, 31% and 28% for 4%, 20% and 40% alcohol respectively in the fasting state;  $C_{max}$  was less affected in the fed state with increases at 14%, 14% and 10%, respectively. The observed variation in  $C_{max}$  is consistent with inter-subject variability associated with the use of immediate-release opioids. Median  $T_{max}$  in the presence/absence of alcohol remains between 12-16 hours. No effect was seen on AUC values both in the fed and fasted state. Due to the OROS<sup>®</sup> technology in JURNISTA<sup>®</sup>, the extended-release properties of JURNISTA<sup>®</sup> are maintained in the presence of alcohol. However, concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

### **Drug-Food Interactions**

No effects on the pharmacokinetics of JURNISTA<sup>®</sup> were observed with administration of a high fat meal. JURNISTA<sup>®</sup> can be taken with and without food.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

## **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

## **Drug-Lifestyle Interactions**

The concomitant use of alcohol should be avoided. Alcohol increases the sedative effect of hydromorphone.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

- Safe and effective administration of JURNISTA<sup>®</sup> to patients with pain depends upon a comprehensive assessment of the patient. The nature of the pain, as well as the patient's medical and analgesic history will affect the selection of the dose. Owing to the varied response to opioids observed between individuals, it is recommended that all patients be started at the lowest possible dose of opioid therapy and titrated to an adequate level of analgesia, balanced against acceptable adverse reactions. The lowest titration increment for JURNISTA<sup>®</sup> is 4 mg.
- **JURNISTA<sup>®</sup> must be swallowed whole. Do not chew, divide, or crush the tablet. Taking broken or crushed tablets could lead to the uncontrolled release and rapid absorption of a potentially fatal dose of hydromorphone.**
- **Tablet strengths of 16 mg and higher are only for opioid-tolerant patients requiring hydromorphone equivalent dosages of 16 mg or higher per day. These doses may lead to severe medical consequences, including fatal respiratory depression, in patients not previously exposed to similar daily doses of opioids.**
- Appropriate prophylaxis for known adverse reactions should be considered. For example, the prescription of antiemetics for nausea and vomiting, and an appropriate regimen of bowel management for constipation (stool softeners, laxatives etc.) should be considered.

### **Recommended Dose and Dosage Adjustment**

The controlled-release nature of the formulation allows JURNISTA<sup>®</sup> to be administered once every 24 hours. JURNISTA<sup>®</sup> tablets should be taken at approximately the same time each day with a glass of water.

JURNISTA<sup>®</sup> tablets can be taken with or without food. JURNISTA<sup>®</sup> should not be taken more than once every 24 hours.

### **Dose Initiation**

#### • Patients Currently Not Routinely Receiving Opioids

Because it takes 13–16 hours for JURNISTA<sup>®</sup> to reach its maximum drug release, it is recommended to begin treatment with a conventional immediate-release preparation (e.g. immediate-release morphine or immediate-release hydromorphone). Once the patient achieves a

steady balance between pain control and adverse reactions, the patient can be converted to the appropriate total daily dose of JURNISTA<sup>®</sup>.

The initial dose in patients who are opioid naïve or receiving low intermittent doses of weak opioid analgesics - less than 40 mg daily oral morphine equivalents - should be 4 mg every 24 hours. If the physician, based on clinical judgement, decides that a higher initial dose is warranted, 8 mg every 24 hours should not be exceeded. The dose may be titrated upwards or downwards, if required, in increments of either 4 or 8 mg depending on response and supplementary analgesic requirements.

- Patients Currently Receiving Opioids Regularly  
**Discontinue all other around-the-clock opioid analgesic medications when JURNISTA<sup>®</sup> therapy is initiated.**

In patients currently taking opioid analgesics, the starting dose of JURNISTA<sup>®</sup> should be based on the prior daily opioid dose, using standard equianalgesic ratios. For opioids other than morphine, first estimate the equivalent total daily dose of morphine, then use Table 1.4 to determine the equivalent total daily dose of JURNISTA<sup>®</sup>.

**Table 1.4: Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of JURNISTA<sup>®</sup> <sup>a</sup>**

<b>(mg/day Prior Opioid x Factor = mg/day JURNISTA<sup>®</sup>)</b>	
<b>mg/day of Prior Opioid</b>	<b>Multiplication (factor) to obtain mg/day of JURNISTA<sup>®</sup></b>
Morphine	0.2
Hydromorphone	1

<sup>a</sup> conversion factors used in JURNISTA<sup>®</sup> clinical trials

No fixed conversion ratio is likely to be satisfactory in all patients, due to individual patient and formulation differences. Therefore, conversion to the recommended starting dose of JURNISTA<sup>®</sup> followed by close patient monitoring and titration should be done.

Immediate-release hydromorphone daily dose or converted hydromorphone equivalent doses should be rounded down to the closest dose of JURNISTA<sup>®</sup> available, and given once a day.

JURNISTA<sup>®</sup> may be used with usual doses of non-opioid analgesics and analgesic adjuvants.

### **Individualization of Dosage and Maintenance of Therapy**

After the initiation of therapy with JURNISTA<sup>®</sup>, 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 stabilize, the dosage should not be increased more frequently than every two days. As a guideline, dosage increases of 25%-75% of the current daily dose of JURNISTA<sup>®</sup> should be considered for each titration step. Once patients become stable on a selected once-daily dose of JURNISTA<sup>®</sup>, 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.

Some patients may require periodic supplemental doses of short-acting analgesic for “breakthrough” pain. The initial individual supplemental analgesia doses should generally not exceed 10% to 25% of the 24-hour JURNISTA<sup>®</sup> dose.

#### Use in Children and Adolescents

JURNISTA<sup>®</sup> is not recommended for use in children and adolescents below age 18 as dosage requirements for the safe and efficacious use of JURNISTA<sup>®</sup> have not been established for this patient population.

#### Use in the Elderly

The medical setting of the elderly is often complex. Therefore, treatment with JURNISTA<sup>®</sup> should be initiated cautiously at a reduced initial dose (see **WARNINGS AND PRECAUTIONS, Special Populations**).

#### Renal and Hepatic Impairment

Following single-dose 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 elimination half-life was unaltered.
- In patients with moderate renal insufficiency (creatinine clearance of 40-60 mL/min), exposure (plasma AUC) to hydromorphone was approximately 2 times higher than in those with normal renal function, and 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 elimination half-life 3 times longer.

Therefore, 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.

#### **Cessation of Therapy**

In patients who are physically dependent on opioids and receiving daily administration of hydromorphone, abrupt discontinuation of treatment with JURNISTA<sup>®</sup> will result in symptoms of withdrawal syndrome. Therefore, if cessation of therapy with JURNISTA<sup>®</sup> is indicated in patients, a gradual downward titration in small increments, such as in steps of 50%, every 2 days is recommended 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<sup>®</sup> dose reduction, or before converting to an equianalgesic dose of another opioid to continue tapering.

## **Missed Dose**

Patients should be advised not to take extra tablets or a double dose to make up for a missed dose. JURNISTA<sup>®</sup> should be taken once approximately every 24 hours.

## **Administration**

JURNISTA<sup>®</sup> tablets should be swallowed whole with a glass of water, at approximately the same time each day. They should never be chewed, divided, or crushed.

## **OVERDOSAGE**

<p><b>For management of a suspected drug overdose, contact your regional Poison Control Centre.</b></p>
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## **Symptoms**

Opioid overdose 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 overdose apnea, circulatory collapse, cardiac arrest and death may occur.

## **Treatment**

In the treatment of overdose, primary attention should be given to the re-establishment of adequate respiratory exchange by keeping the airway open and instituting assisted or controlled ventilation. If 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 edema, which potentially accompany overdose. Cardiac arrest and arrhythmias may require cardiac massage or defibrillation.

In cases of severe overdose, specific antidotes such as naloxone should be used to manage respiratory depression (see the prescribing information for the specific opioid antagonist for details of proper use). The effect of naloxone is relatively short; therefore, the patient should be carefully monitored until respiration has stabilized. JURNISTA<sup>®</sup> 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 caused by 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.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Hydromorphone, a semi-synthetic morphine derivative, is a hydrogenated ketone of morphine. Hydromorphone is principally an agonist of  $\mu$ -receptors, showing a weak affinity for  $\kappa$ -receptors. Comparing relative binding affinity for  $\mu$ - and  $\kappa$ -opioid receptors, hydromorphone binds more specifically to  $\mu$ -receptors than structurally related morphine. Hydromorphone produces diverse pharmacological effects by binding to opioid receptors in the CNS and other tissues.

### **Pharmacodynamics**

As with all opioid analgesics, hydromorphone exerts its principal pharmacological effects on the CNS and smooth muscle, including the gastrointestinal tract. These effects are expressed and modulated by binding to specific opioid receptors. Hydromorphone is principally an agonist of  $\mu$ -receptors, showing a weak affinity for  $\kappa$ -receptors. Analgesia occurs as a consequence of the binding of hydromorphone to the  $\mu$ -receptors of the CNS. Although estimates vary (from 2 to 10 times), oral hydromorphone appears to be approximately 5 times as potent (by weight) as morphine. Respiratory depression occurs principally by direct action on the cerebral respiratory control centres. Opioids may cause nausea and vomiting due to direct stimulation of the chemoreceptor for emesis in the posterior area of the medulla.

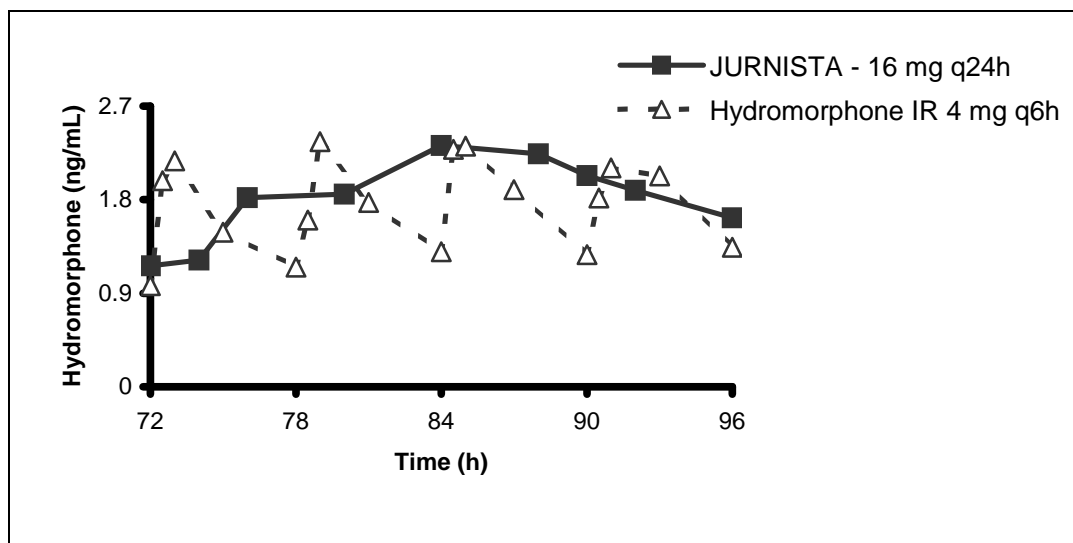
### **Pharmacokinetics**

#### **Absorption**

Following a single oral dose of JURNISTA<sup>®</sup> prolonged-release tablets, plasma concentrations gradually increase over 6 to 8 hours, and thereafter concentrations are sustained for approximately 18 to 24 hours post-dose; the mean  $T_{max}$  values were approximately 13 to 16 hours. This demonstrates that hydromorphone is released in a controlled manner consistent with once-daily dosing. The mean absolute bioavailability of hydromorphone from JURNISTA<sup>®</sup> ranged from 22% to 26%.

Steady-state plasma concentrations are approximately twice those observed following the first dose, and steady state is reached by the fourth dose of JURNISTA<sup>®</sup>. No time-dependent change in pharmacokinetics was seen with multiple dosing. At steady state, JURNISTA<sup>®</sup> 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 diminished 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 was lower with JURNISTA<sup>®</sup> (83%) as compared to the overall fluctuations of the immediate-release tablet (147%) (see Figure 1.1). At steady state, hydromorphone AUC for JURNISTA<sup>®</sup> is equivalent to that observed for the immediate-release tablet dosed four times daily.

**Figure 1.1**  
Steady-State Plasma Hydromorphone Concentration-Time Curves



Linear pharmacokinetics has been demonstrated for JURNISTA<sup>®</sup> over the dose range 4 to 64 mg, with a dose-proportional increase in plasma concentrations ( $C_{max}$ ) and overall exposure ( $AUC_{(0-48h)}$  and  $AUC_{(0-inf)}$ ).

Studies with immediate-release hydromorphone indicated that food delayed the rate of absorption of hydromorphone, resulting in a 25% decrease in  $C_{max}$  and a 24% increase in AUC. The pharmacokinetics of JURNISTA<sup>®</sup> (single dose 16 mg) was not affected by a high-fat meal. Bioequivalence (AUC and  $C_{max}$ ) was demonstrated under fast and fed conditions. Therefore, JURNISTA<sup>®</sup> can be administered with or without food (see **DETAILED PHARMACOLOGY**).

In a study in patients with chronic pain who had been titrated with JURNISTA<sup>®</sup> to control pain, plasma concentrations began to rise about two hours post-dose, achieving maximal values over a broad and sustained time period, similar to that observed with JURNISTA<sup>®</sup> in healthy subjects. Pharmacokinetic/pharmacodynamic analysis indicated that, in general, rising and falling plasma hydromorphone concentrations correlated with decreasing and increasing pain, respectively.

In a study comparing hydromorphone absorption from JURNISTA<sup>®</sup> taken with no alcohol and 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 12-16 hours and with 0% alcohol was 16 hours. No effect was seen on AUC values both in the fed and fasted state. Concomitant use of alcohol should be avoided. Due to the OROS<sup>®</sup> technology in JURNISTA<sup>®</sup>, the prolonged-release properties of JURNISTA<sup>®</sup> are maintained in the presence of alcohol. For the pharmacodynamic interactions (see **WARNINGS AND PRECAUTIONS, General**).

### Distribution

The mean extent of binding of hydromorphone to human plasma proteins was determined to be < 30% in an in vitro study.

## **Metabolism**

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.

First-pass metabolism is rapid and extensive. The elimination half-life for hydromorphone is approximately 2 hours.

## **Excretion**

Following a single dose of [<sup>14</sup>C]-hydromorphone, hydromorphone and total radiolabelled material disappear from the plasma in approximately 8 hours after dosing, indicating relatively rapid clearance of all drug-related material from the plasma.

Most of the administered hydromorphone dose is excreted as metabolites, with urine as the major route of excretion, accounting for 75% of the administered dose. Approximately 7% and 1% of the dose are excreted as unchanged hydromorphone in urine and feces, respectively.

## **Special Populations and Conditions**

### **Pediatrics**

Very limited data (in published literature) suggest that the pharmacokinetic profile of hydromorphone in children is comparable to that in adults. No clinical studies with JURNISTA<sup>®</sup> have been conducted in children.

### **Geriatrics**

The effect of age on the single-dose pharmacokinetics of immediate-release hydromorphone resulted in a 14% decrease in  $C_{max}$  and a modest increase (11%) in AUC in elderly subjects compared to young subjects. No difference in  $T_{max}$  was observed. 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 (see **DOSAGE AND ADMINISTRATION**).

### **Gender**

Plasma concentrations and pharmacokinetic parameters following administration of JURNISTA<sup>®</sup> are comparable in male and female subjects.

### **Race**

Population pharmacokinetic analysis revealed no evidence of race-related differences in the pharmacokinetics of hydromorphone following JURNISTA<sup>®</sup> administration.

### **Hepatic Insufficiency**

In studies that used single oral dosing with conventional immediate-release hydromorphone tablets, hepatic impairment reduced the first-pass metabolism of hydromorphone such that four-fold increases in plasma levels of hydromorphone were seen in subjects with moderate hepatic dysfunction. See **DOSAGE AND ADMINISTRATION** for recommendations on dosage.

### **Renal Insufficiency**

Renal impairment affected the pharmacokinetics of hydromorphone and its metabolites hydromorphone 3-glucuronide and hydromorphone 3-sulphate 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 impairment, respectively. There were also substantial changes in hydromorphone 3-glucuronide elimination kinetics for the severe impairment group, although hemodialysis was effective at reducing plasma levels of both hydromorphone and its metabolites. See **DOSAGE AND ADMINISTRATION** for recommendations on dosage.

### **STORAGE AND STABILITY**

JURNISTA<sup>®</sup> hydromorphone hydrochloride prolonged-release tablets should be stored between 15 and 25°C.

### **SPECIAL HANDLING INSTRUCTIONS**

N/A

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

JURNISTA<sup>®</sup> tablets use the oral osmotic pump (OROS<sup>®</sup>) Push-Pull<sup>™</sup> technology to deliver hydromorphone by a membrane-controlled, osmotically activated process at a constant, controlled rate over 24 hours. All JURNISTA<sup>®</sup> dosage strengths have qualitatively similar formulations, and are designed to deliver proportionately similar amounts of hydromorphone over the 24-hour dosing period.

The JURNISTA<sup>®</sup> tablet is a small, round tablet with hydromorphone hydrochloride as the active ingredient. The JURNISTA<sup>®</sup> tablet is composed of a bilayer tablet core surrounded by a semi-permeable membrane, and coloured and clear overcoating.

Each JURNISTA<sup>®</sup> 4 mg prolonged-release tablet contains 4.36 mg and delivers 4 mg hydromorphone HCl, equivalent to 3.56 mg hydromorphone base. JURNISTA<sup>®</sup> 4 mg is a pale beige, round, biconvex tablet, with 'HM 4' printed in black ink on one side.

Each JURNISTA<sup>®</sup> 8 mg prolonged-release tablet contains 8.72 mg and delivers 8 mg hydromorphone HCl, equivalent to 7.12 mg hydromorphone base. JURNISTA<sup>®</sup> 8 mg is a red, round, biconvex tablet, with 'HM 8' printed in black ink on one side.

Each JURNISTA<sup>®</sup> 16 mg prolonged-release tablet contains 16.35 mg and delivers 16 mg hydromorphone HCl, equivalent to 14.24 mg of hydromorphone base. JURNISTA<sup>®</sup> 16 mg is a yellow, round, biconvex tablet, with 'HM 16' printed in black ink on one side.

Each JURNISTA<sup>®</sup> 32 mg prolonged-release tablet contains and delivers 32.00 mg hydromorphone HCl, equivalent to 28.48 mg of hydromorphone base. JURNISTA<sup>®</sup> 32 mg is a white, round, biconvex tablet, with 'HM 32' printed in black ink on one side.

The following are the excipients for JURNISTA<sup>®</sup> prolonged-release tablets:

butyl hydroxytoluene, cellulose acetate, glycerol triacetate (8 mg, 16 mg, and 32 mg), iron oxide black, ferric oxide red (4 mg and 8 mg), ferric oxide yellow (4 mg, 16 mg and 32 mg), hypromellose, lactose anhydrous, lactose monohydrate (8 mg, 16 mg, and 32 mg), macrogol, magnesium stearate, polyethylene oxide, povidone, propylene glycol, sodium chloride, and titanium dioxide.

JURNISTA<sup>®</sup> may contain traces of sodium metabisulfite.

JURNISTA<sup>®</sup> prolonged-release tablets are packaged in PVC/Aclar aluminum blisters.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

**Proper Name:** Hydromorphone hydrochloride

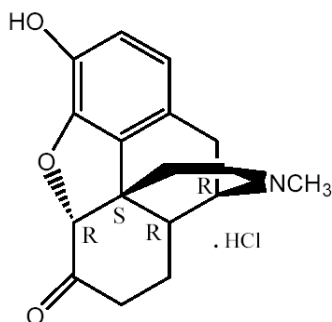
**Chemical Name:** 4,5 $\alpha$ -epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride

#### **Molecular Formula and Molecular Mass:**

Molecular formula: C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>·HCl

Molecular mass: 321.8

#### **Structural Formula:**



#### **Physicochemical properties:**

Hydromorphone hydrochloride is a white or almost white crystalline powder that is freely soluble in water, very slightly soluble in ethanol (96%) and practically insoluble in methylene chloride. Hydromorphone hydrochloride has a pKa of 8.1 for the deprotonation of the NH<sup>+</sup> group and a pKa: 9.6 for the deprotonation of the phenolic group.

The specific rotation for hydromorphone hydrochloride at 20°C has a range of -136° to -140°.

## CLINICAL TRIALS

JURNISTA<sup>®</sup> was studied in several clinical pain models including patients with cancer pain, osteoarthritis, low back pain, and other non-cancer chronic pain (see **REFERENCES, Clinical**). The safety profile of JURNISTA<sup>®</sup> from these studies was consistent with that of a strong opioid agonist (see **ADVERSE REACTIONS**).

### Placebo-Controlled Studies

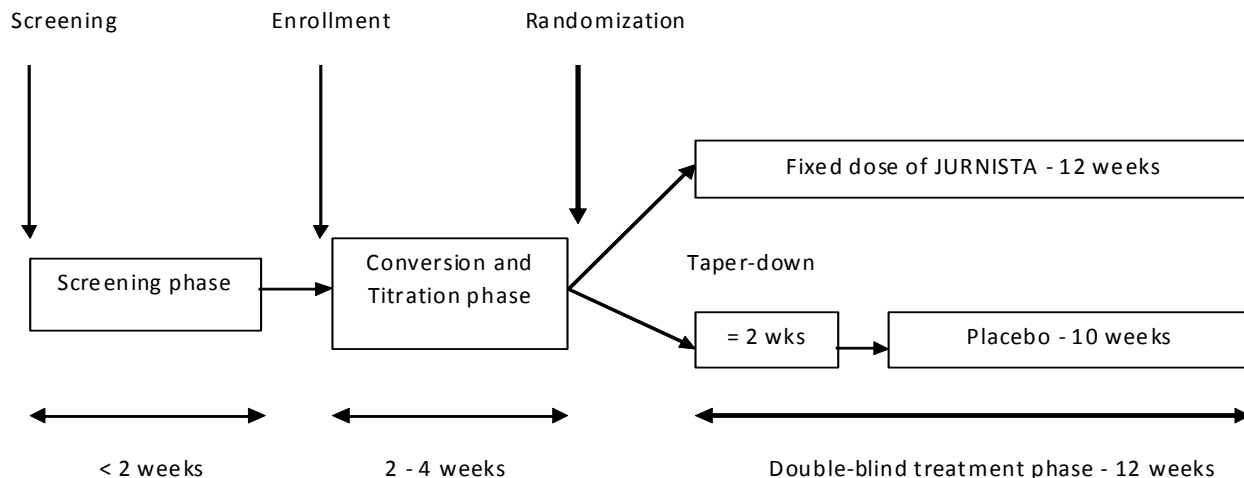
**Table 2.1: Summary of Patient Demographics for JURNISTA<sup>®</sup> Clinical Trials**

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 <sup>®</sup> 8 mg, 16 mg, or placebo qd with 12 weeks 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
NMT 1077-301	Placebo-controlled, double-blind study with a conversion and titration phase (C&T), and a double-blind phase (DB)	Oral administration of JURNISTA <sup>®</sup> 12 to 64 mg, or placebo qd	C&T phase: n= 447; DB phase: n= 266 (ITT: 133 for JURNISTA <sup>®</sup> , 133 for placebo)	49.0 y (23,75)	C&T: 227 M, 220 F;  DB: 132 M, 134 F

### **Low Back Pain**

#### Study Demographics and Trial Design

JURNISTA<sup>®</sup> was investigated in Study NMT01077-301, a double-blind, placebo-controlled, randomized withdrawal study in 266 opioid tolerant patients with moderate to severe chronic Low Back Pain. Patients who were stabilized previously with an immediate release strong opioid entered an open-label conversion and titration phase with JURNISTA<sup>®</sup>. The starting dose for conversion was approximately 75% of their total daily morphine equivalent dose. Patients were dosed with JURNISTA<sup>®</sup> once daily until adequate pain control was achieved, balanced against acceptable adverse reactions. Patients who achieved a stable dose entered a 12-week, double-blind, placebo-controlled, randomized treatment phase. Mean daily dose at randomization was 37.8 mg/day (median 32.0 mg/day, range of 12 mg/day - 64 mg/day). During the double-blind treatment phase, patients randomized to JURNISTA<sup>®</sup> continued with the stable dose achieved in the conversion and titration phase of the study. Patients randomized to placebo received JURNISTA<sup>®</sup> and matching placebo in doses tapering from the stable dose achieved in conversion and titration. Immediate release hydromorphone was provided for analgesia rescue throughout the JURNISTA<sup>®</sup> Conversion and Titration phase and double-blind treatment phase.



The primary efficacy outcome parameter, change in mean pain intensity on the 11-point Numeric Rating Scale (NRS) from baseline to Week 12, was 0.2 (median, range -5, 5) on JURNISTA<sup>®</sup> versus 1.6 (median, range -3, 7) on placebo ( $p < 0.001$ ). Results from secondary outcome parameters based on change from baseline to Week 12, such as patient global assessment, and Roland Morris Disability Questionnaire were supportive. During the 12-week double-blind withdrawal study phase, the percentage of drop-outs was 66.9% in patients on placebo versus 50.4% in patient on JURNISTA<sup>®</sup> ( $p < 0.01$ ).

### Comparative Bioavailability Studies

Comparative bioavailability between JURNISTA<sup>®</sup> and Immediate-Release (IR) hydromorphone tablet has been evaluated in single- and multi-dose studies. To block the opioid effects of hydromorphone during study treatment, each subject received oral naltrexone 50 mg as an opioid antagonist in each treatment period.

**Study PAI-1008** was a randomized, open-label, three-way crossover study conducted in 30 healthy male and female adult subjects. This study assessed the relative bioavailability of hydromorphone following the oral administration of a daily dose of JURNISTA<sup>®</sup> (OROS hydromorphone) 16 mg and DILAUDID<sup>®</sup> (IR hydromorphone) 4 mg q6h. Additionally, the effects of a high-fat meal on the pharmacokinetics of JURNISTA<sup>®</sup> 16 mg were also assessed.

The following table summarizes the pharmacokinetic parameters for JURNISTA<sup>®</sup> and IR hydromorphone under fasted condition.

JURNISTA <sup>®</sup> 16 mg qd Hydromorphone IR 4 mg q6h From measured data Geometric Mean Arithmetic Mean (±SD)				
Parameter	JURNISTA <sup>®</sup>	IR Hydromorphone	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>last</sub> (ng.h/mL)*	44.696	42.836	104.3	94.9 - 114.7
AUC <sub>∞</sub> (ng.h/mL)*	47.578	44.436	107.1	97.0 – 118.1
C <sub>max</sub> <sup>ε</sup> (ng/mL)	1.89 (0.484)	3.57 (1.46)		
T <sub>max</sub> <sup>§</sup> (h)	17.9 (6.01- 24.2)	18.5 (18.5-20.0)		
T <sub>1/2</sub> <sup>ε</sup> (h)	14.4 (6.04)	12.7 (3.43)		

\*AUC values are expressed as the geometric mean

§ Expressed as the arithmetic median (range)

ε Expressed as the arithmetic mean (SD)

The JURNISTA<sup>®</sup> and IR hydromorphone formulations administered under fasting conditions were bioequivalent with respect to AUC<sub>last</sub> and AUC<sub>∞</sub>. Additionally, the JURNISTA<sup>®</sup> formulation administered under fasting and fed conditions were bioequivalent with respect to C<sub>max</sub> and AUC.

**Study PAI-1009** was a randomized, open-label, multi-dose, two-way crossover study conducted in 29 healthy male and female adult subjects. This study assessed the steady-state relative bioavailability and pharmacokinetics of hydromorphone following oral administration of JURNISTA<sup>®</sup> (OROS hydromorphone) 16 mg qd and DILAUDID<sup>®</sup> (IR hydromorphone) 4 mg q6h for five days. The following table summarizes the multiple-dose pharmacokinetic parameters for JURNISTA<sup>®</sup> and IR hydromorphone.

JURNISTA <sup>®</sup> 16 mg qd Hydromorphone IR 4 mg q6h From measured data Geometric Mean Arithmetic Mean (±SD)				
Parameter	JURNISTA <sup>®</sup>	IR Dilaudid	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>0-τ</sub> * (ng.h/mL)‡	55.677	52.915	105.2	99.9 – 110.8
C <sub>max,ss</sub> <sup>ε</sup> (ng/mL)	3.54 (0.959)	5.28 (1.37)		
C <sub>min,ss</sub> <sup>ε</sup> (ng/mL)	2.15 (0.872)	1.47 (0.417)		
C <sub>ave,ss</sub> <sup>ε</sup> (ng/mL)	2.40 (0.678)	2.28 (0.618)		
t <sub>max,ss</sub> <sup>§</sup> (h)	11.9 (5.92 -24.2)	7.00 (0.500-18.8)		
Flux (%)	60.5 (41.1)	172 (57.6)		

\*AUC values are expressed in geometric mean

ε Expressed as the arithmetic mean (±SD)

§ Expressed as median (range)

JURNISTA<sup>®</sup> 16 mg qd attained steady-state concentrations by Day 4 and was shown to maintain steady-state hydromorphone plasma concentrations within the same range as IR hydromorphone 4mg q6h tablets, although with reduced plasma level fluctuation.

## DETAILED PHARMACOLOGY

### Pharmacodynamics

Hydromorphone is an opioid analgesic with ATC code: N02AA03.

Hydromorphone hydrochloride is a hydrogenated ketone of morphine. *In vitro* assays demonstrate that hydromorphone binds to the opioid  $\mu$ -receptor with high affinity with  $K_i = 0.24$  nM, which is 7 times that of morphine ( $K_i = 1.8$  nM). In a comparison of the binding affinity to the  $\mu$ -receptor, the selectivity of hydromorphone is 60-fold versus the  $\delta$ -receptor, and 52-fold versus the  $\kappa$ -opioid receptor, while morphine binding affinity is 89-fold versus the  $\delta$ -receptor and 26-fold versus the  $\kappa$ -opioid receptor. Whereas analgesia appeared to correlate with  $\mu$ -binding affinity, activation of  $\kappa$ -receptors is considered to be responsible, among other adverse effects, for cardiac changes, such as arrhythmias during ischemia/reperfusion seen in the isolated rat heart.

## TOXICOLOGY

The potential toxicity of hydromorphone has been evaluated in single-dose, repeat-dose, mutagenicity, reproduction and developmental studies. The oral tolerability of JURNISTA<sup>®</sup> was evaluated in a repeat-dose study and the intravenous toxicity of the major polyethylene oxide excipients was evaluated in single and repeat dose studies.

### Single-Dose Toxicity

Summary of the acute toxicity studies is presented in the following table. The acute intoxication in rodents is characterised by respiratory depression and CNS depression in terms of sedation, agitation, effects on eyes as well as weakness and uncoordinated muscle movements.

**Table 2.2: Single-Dose Toxicity**

Species (Strain) / Sex & No./Dose Group	Route / Duration / Dose (mg/kg)	Noteworthy Findings / NOAEL <sup>a</sup> (mg <sup>#</sup> /kg)
Mouse (NMRI) / 5M, 5F	Single dose/ Oral (gavage) 0, 46.4, 147, 215, 261	Straub tail, hyperactivity, stiff gait, rough coat, ataxia / M: 46.4, F: 147
Mouse (NMRI) / 5M, 5F	Single dose/ Intravenous / 0, 14.7, 21.5, 31.6, 46.4, 68.1, 100.0	Straub tail, hyperactivity, intermittent apathy, stiff gait, exophthalmos, clonic convulsions, ataxia / M: 46.4, F: 68.1
Rat (Wistar) / 5M, 5F	Single dose / Oral (gavage) / 0, 1.0, 10.0, 21.5, 31.6	Exophthalmos, opisthotonus, hyperphagia of bedding, lassitude, gnawing of tail / M: 10, F: 21.5
Rat (Wistar) / 5M, 5F	Single dose / Intravenous / 0, 1.0, 4.64, 6.81	Prone position, stiffness, lassitude, exophthalmos, flat respiration, impaired grip strength/pinna reflex/toe pinch reflex, red discoloration of paws, hyperactivity, compulsive grooming / M & F: 1.0

<sup>a</sup> NOAEL: No Observed Adverse Effect Level

<sup>#</sup> expressed as hydromorphone base

## **Repeat-Dose Toxicity**

### **Hydromorphone**

In mice, repeated oral administration of hydromorphone resulted in increased activity, rough coat, Straub tail, inappetence and in females only, vocalization. Following repeat-dose administration to rats, there were no signs of respiratory depression; however, distinct symptoms of CNS depression predominated. In addition to the findings of acute intoxication, the animals showed abnormal behaviour (i.e. aggressiveness), inappetence (i.e. reduction of food consumption and body weight), and effects on eyes (i.e. mydriasis) and gastrointestinal tract (i.e. diarrhea), as well as rigid posture indicating uncoordinated muscle movements.

The frequently observed side effects in repeatedly dosed dogs included respiratory depression and CNS depression in terms of sedation, vomiting, salivation, abnormal behaviour, hypothermia, inappetence, effects on eyes and gastrointestinal tract, as well as uncoordinated muscle movements (i.e. imbalance, abnormal posture/recumbency or tremor). To a lesser degree, circulatory depression in terms of a decrease in blood pressure (probably due to peripheral vasodilation) and a compensatory increase in heart rate was also observed.

Following chronic administration of oral hydromorphone to rats (for at least 39 weeks), there were signs of tolerance to the treatment-related effects, but no symptoms of withdrawal were observed in the course of the study. A summary for the pivotal repeated-dose studies for hydromorphone is provided in Table 2.3

### **OROS hydromorphone: Gastrointestinal Tolerability**

The gastrointestinal tolerability of 30-day daily administration of OROS Hydromorphone was assessed in dogs in comparison with oral immediate-release hydromorphone at 64 mg/day. The OROS Hydromorphone dosage form was as equally well tolerated as immediate-release hydromorphone, at similar exposures, with no gastric irritation apparent.

### **Polyethylene Oxide: Excipient**

Polyethylene oxides, POLYOX™ 200K and POLYOX™ 2000K, are the major OROS® tablet excipients that provide the osmotic engine for the OROS® controlled-release mechanism. Both POLYOX 200K and POLYOX 2000K are metabolically inert and well tolerated by the oral route at doses up to 2000 mg/kg/day over extended periods of administration.

Due to the known potential for parenteral abuse of hydromorphone, in particular via the intravenous route, the toxicologic risk presented by inadvertent intravenous co-administration of the OROS® hydromorphone tablet polyethylene oxide excipients was investigated. When administered intravenously to rats, both forms of POLYOX were found to be poorly tolerated, while POLYOX 2000K caused mortality at the highest doses tested, supporting findings reported in literature . Both forms of POLYOX remained in the circulation at high concentrations for extended periods, consistent with their high molecular weights and lack of metabolic clearance pathway.

**Table 2.3: Repeat Dose Toxicity**

Species and Strain/ Sex / No./Group	Duration of Dosing / Method of Administration/ Doses <sup>#</sup> (mg/kg) or (units) <sup>#</sup>	Noteworthy Findings / NOAEL <sup>a</sup> (mg/kg)
Rat (Wistar) / 10M, 10F	4 weeks / Oral (gavage) / 0, 3.5, 7.0, 14.0	No mortality. In all dose groups, M & F: signif. decrease in body weight change; non-signif. decrease in food consumption; neurobehavioural clinical signs including hyperactivity, compulsive chewing; at 7 mg/kg and above, expophthalmus; at 14 mg/kg, alopecia and ophthalmic observations 9/10M, 4/10F. From 3.5 mg/kg in M & F, signif. decreased triglycerides and urea; increased bilirubin. From 3.5 mg/kg: signif. increased (M > F) organ weights over controls: brain, heart, liver, adrenal glands, testes (M), decreased thymus. No significant effects in 4-week recovery group. / M, F: 3.5
Rat (Wistar) / 20M, 20F	27 weeks / Oral (gavage) / 0, 3.5, 7.0, 14.0	One M died in each of 3.5 and 14 mg/kg groups. In all dose groups, M & F: decrease in body weight change (M > F); neurobehavioural clinical signs including hyperactivity, compulsive chewing; self-mutilation, sedation, lassitude, mydriasis, diarrhea, expophthalmus, alopecia, rough coat; from 7.0 mg/kg, aggressiveness, rigid posture, and increased ophthalmic observations (lens opacities). From 3.5 in M > F, occasional signif. increased K, decreased Na, Ca, protein, triglycerides. From 3.5 mg/kg: signif. increased (M > F) organ weights over controls: brain, heart, liver, adrenal glands, testes (M). From 3.5 mg/kg, gross pathology showed hepatocellular atrophy in M with increasing incidence, retinal atrophy; from 7 mg/kg minimal adnexal atrophy; at 14 mg/kg lungs showed granulomas, confirmed histopathologically. Occasional increased organ weights remained significant effects in recovery group. / M, F: 3.5
Dog (Beagle) / 4M, 4F	30 days / Oral JURNISTA <sup>®</sup> (tablets) / 0, 8, 64 mg/animal Dilaudid (tablets) / 64 (2 x 32) mg/animal	One F dosed with Dil-IR died. Dil-IR M & F: excess salivation; increased fasting glucose. In F in all groups and M at 64 mg OHM and Dil-IR, vomiting, unformed stool, decreased activity, tremors, ophthalmoscopy findings. / M, F: 8
Dog (Beagle) / 4M, 4F	4 weeks / Oral (capsules) / 0, 1.75, 3.5, 7	No mortality. From 1.75 mg/kg, F: signif. decreased body weight. At 7 mg/kg, week 4, M & F: signif. decreased mean arterial blood pressure, increased heart rate; sl. increased Na; increased CL. At 7 mg/kg, M: signif. decreased spleen weight. In gross pathology, from 3.5 mg/kg: diminished size thymus; enlarged adrenals, liver; at 7.0 mg/kg: diminished size prostate; emaciation/dehydration noted. At 7 mg/kg histopathology showed increased gastric mucus, focal adrenocortical hypertrophy, increased cortical atrophy. / M, F: 3.5
Dog (Beagle) / 7M, 7F	39 weeks / Oral (capsules) / 0, 1.75, 4.0, 9	No mortality. From 1.75 mg/kg, M & F: clinical observations of sedated, foamy salivation, incomplete food consumption, ventral recumbency. At week 38, from 1.75 mg/kg, M & F: signif. increased glucose; decreased ALT (except 1.75 & 4 mg/kg M). From 4.0, M: signif. increased pituitary gland weight. From 1.75, M & F: histopathology showed many observations in 1 or 2 animals, with no clear dose-related pattern of incidence except granulocytic infiltrates in kidneys observed in 3-4 animals per group. / M, F: 9

<sup>a</sup> NOAEL: No Observed Adverse Effect Level

## **Mutagenic Potential**

Hydromorphone under in vitro and in vivo conditions was neither mutagenic nor clastogenic. Details of the studies are provided in Table 2.4.

**Table 2.4: Genotoxicity**

<b>Type of Test / Species and Strain / No./Group</b>	<b>Duration of Dosing / Method of Administration / Concentrations (units) / Doses (mg/kg) #</b>	<b>Noteworthy Findings</b>
Ames Test: Reverse Mutation Assay / <i>Salmonella typhimurium</i> (TA98, TA100, TA1535, TA1537)	<i>In vitro</i> / 100–5000 µL/plate	No mutagenicity No cytotoxic effects
Ames Test: Reverse Mutation Assay / <i>Salmonella typhimurium</i> (TA98, TA100, TA1535, TA1537, TA102)	<i>In vitro</i> / 33–5000 µL/plate	No mutagenicity Assay #1: Slight effects without S9 mix in TA100 at 5000 µg/plate Assay #2: Slight effects without S9 mix in TA1537 at 5000 µg/plate
Chromosome Aberration Test / Human lymphocytes /	Single dose / Oral (gavage) / 400–3200 µg/mL	No mutagenicity or clastogenicity Assay #1: Only slightly reduced mitotic index (MI) at top dose without S9 mix (3200µg/mL). Assay #2: Distinctly reduced MI after 22.5h and 46h continuous treatment without S9 mix only observed at 1600 µg/mL.
Micronucleus Assay/ Mouse (NMRI) / 6M, 6F	Single dose / Oral (gavage)/ 10, 33.3, 100 (mg/mL)	No genotoxicity effects observed MTD: 100 mg/kg, 3/24 animals died prematurely at this dose. Cytotoxic effect only at 100 mg/kg at 48h.

# Doses in mg of hydromorphone base

## **Carcinogenesis and Mutagenesis**

Long-term carcinogenicity studies have not been performed with JURNISTA®

## **Reproduction and Developmental Studies**

In reproductive and developmental studies in rats and rabbits, no effects on male or female fertility or sperm parameters were observed in rats at oral hydromorphone doses of up to 6.25 mg/kg/day. No effect was observed on female reproductive parameters at oral doses of up to 25 mg/kg/day in rabbits, or 3.13 mg/kg/day in rats. In rats, a slight but statistically significant reduction in implantations was observed at 6.25 mg/kg/day, a dose level that produced maternal toxicity (weight loss) during the mating period. There was no evidence of teratogenicity or toxicity to the developing rat fetus at oral doses of 6.25 mg/kg/day. Plasma exposure (AUC) to hydromorphone at this dose level was 135 ng.hr/mL, approximately 1.5 times the human exposure (AUC) based on the median daily dose. Neonatal viability and survival was reduced in preweaning rats, at the maternal oral daily dose of 6.25 mg/kg. The latter appears to be a class effect of an opioid analgesic. In view of the demonstrated ability of hydromorphone to cross the placental barrier in rats and rabbits and to be excreted in breast milk of rats and humans, hydromorphone (and also other morphine-like drugs) should be used with caution during labour or in nursing mothers. Reproduction and teratology studies are summarized in Table 2.5.

**Table 2.5: Reproductive and Developmental Toxicity**

Type of Study / Species (Strain) / No./Group	Duration of Dosing / Method of Administration / Doses (mg/kg) <sup>#</sup>	Noteworthy Findings / NOAEL <sup>a</sup>
Segment I: Fertility and Early Embryonic Development / Rat (Sprague-Dawley) / 20M, 20F	Males: 28 days pre mating Females: 14 days pre mating to 7 <sup>th</sup> day of gestation / Oral (gavage) / 0, 1.56, 3.13, 6.25	<u>Males</u> : no mortalities. From 1.56 mg/kg: increased restlessness, motor activity and self-mutilation. From 3.13 mg/kg: loss of hair; decreased body weight; slight decrease in spermatids/g testicular tissue. <u>Females</u> : no mortalities. From 1.56 mg/kg: increased restlessness, motor activity. From 3.13 mg/kg: loss of hair; decreased body weight, pre mating & gestational. At 6.25 mg/kg: decreased: mean no. corpora lutea; signif. mean no. implantations; mean no. live conceptuses; NOAEL F <sub>0</sub> M: <1.56 mg/kg; NOAEL F <sub>0</sub> F: <1.56 mg/kg; NOAEL F <sub>1</sub> litters: 3.13 mg/kg
Segment II: Effects on Embryofetal Development / Rat (Sprague-Dawley) / 20F	Females: 11 days (6 <sup>th</sup> to 17 <sup>th</sup> day of gestation) / Oral (gavage) / 0, 1.56, 3.13, 6.25	No mortalities. No fetal abnormalities. From 1.75 mg/kg: signif. decreased body weight, pre mating & gestational. From 3.13 mg/kg: signif. increased restlessness, motor activity, loss of hair; signif. decreased food consumption. At 6.25 mg/kg: signif. decreased mean no. implantations; increased mean % post-implantation loss. NOAEL F <sub>0</sub> F: 1.56 mg/kg; NOAEL F <sub>1</sub> litters: 3.13 mg/kg
Segment II: Effects on Embryofetal Development (non-pivotal) / Rabbit (Himalayan) / 2F (both pregnant)	Females: 14 days (6 <sup>th</sup> to 20 <sup>th</sup> day of gestation) / Oral (gavage) / 0, 1.56, 3.13, 6.25, 12.5	No mortality in dams; no fetal abnormalities. From 1.56 mg/kg: decreased body weight; decreased food consumption. At 12.5 mg/kg: increased resorptions; increased % mean pre-implantation loss; decreased fetal body weight. NOAEL F <sub>0</sub> F: 12.5 mg/kg; NOAEL F <sub>1</sub> litters: >12.5 mg/kg
Segment II: Effects on Embryofetal Development / Rabbit (Himalayan) / 20F	Females: 14 days (6 <sup>th</sup> to 20 <sup>th</sup> day of gestation) / Oral (gavage) / 0, 6.25, 12.5, 25	No mortality in dams; no dose-related fetal abnormalities. From 12.5 mg/kg: reduced motility. At 25 mg/kg: abdominal position, mydriasis, sedation; signif. decreased body weight; signif. decreased food consumption. From 12.5 mg/kg: increased mean % preimplanation loss; decreased fetal body weight. NOAEL F <sub>0</sub> F: 6.25 mg/kg; NOAEL F <sub>1</sub> litters: 25 mg/kg
Segment III: Effects Pre- and Postnatal Development Including Maternal Function / Rat (Sprague-Dawley) / 20F	Females: 27 days (6 <sup>th</sup> day of gestation to 21 <sup>st</sup> day of lactation) / Oral (gavage) / 0, 1.56, 3.13, 6.25	F <sub>0</sub> : One mortality each at 1.56 and 6.25 mg/kg. No abnormal parturition. From 1.56 mg/kg: thin fur. At 3.13 mg/kg: self-mutilation; signif. decreased gestational body weight and food consumption, and lactational food consumption. F <sub>1</sub> litters (preweaning), at 6.25 mg/kg: signif. decreased viability index - mean litter index (%) and overall survival - mean litter index (%); M & F: signif. decreased Day 1 mean body weights. F <sub>1</sub> pups: no clinical signs and no abnormalities; F <sub>2</sub> : No fetal abnormalities NOAEL F <sub>0</sub> F: <1.56 mg/kg ; NOAEL F <sub>1</sub> litters: 1.56 mg/kg; NOAEL F <sub>2</sub> litters: 6.25 mg/kg

<sup>a</sup> NOAEL: No observed adverse effect level

<sup>#</sup> Doses in mg of hydromorphone base

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**PART III: CONSUMER INFORMATION**

**JURNISTA<sup>®\*</sup>**

hydromorphone hydrochloride Prolonged Release Tablets

This leaflet is Part III of a three-part "Product Monograph" published when JURNISTA<sup>®</sup> was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JURNISTA<sup>®</sup> tablets. Contact your doctor or pharmacist if you have any questions about the drug.

**Keep JURNISTA<sup>®</sup> in a safe place away from children and pets. Accidental use by a child is a medical emergency and may result in death. If a child accidentally takes JURNISTA<sup>®</sup>, get emergency help right away.**

Please read this before you start taking JURNISTA<sup>®</sup> tablets. Remember, this information does not take the place of your doctor's instructions.

**WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT JURNISTA<sup>®</sup>?**

- Do not crush, divide, or chew JURNISTA<sup>®</sup> tablets before swallowing. If JURNISTA<sup>®</sup> is taken in this way, hydromorphone will be released too fast. This can lead to serious and life-threatening breathing problems. Life-threatening breathing problems can also happen because of an overdose or if the dose you are using is too high for you. Get emergency medical help immediately if you:
  - have trouble breathing, or have slow or shallow breathing
  - have a slow heartbeat
  - have severe sleepiness
  - have cold, clammy skin
  - feel faint, dizzy, confused, or cannot think, walk, or talk normally
  - have a seizure
  - have hallucinations
- JURNISTA<sup>®</sup> is not for use to treat pain that you only have once in a while ("as needed").
- Take JURNISTA<sup>®</sup> exactly as prescribed by your healthcare provider. Do not take 16 mg or more of JURNISTA<sup>®</sup> every 24 hours unless you are "opioid tolerant". Your doctor will tell you when you are "opioid tolerant" to a certain dose of JURNISTA<sup>®</sup>.
- Never give JURNISTA<sup>®</sup> to anyone else, even if they have the same symptoms you have. It may harm them or even cause death.
- Tell your doctor if you (or a family member) have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- Prevent theft, misuse or abuse. Keep JURNISTA<sup>®</sup> in a safe place to protect it from being stolen.
- After you stop taking JURNISTA<sup>®</sup> you should take the unused tablets to your pharmacist to be destroyed.

**ABOUT THIS MEDICATION**

**What the medication is used for:**

JURNISTA<sup>®</sup> belongs to a class of painkiller drugs commonly referred to as opioids or narcotics and includes codeine, fentanyl, oxycodone and morphine. Your doctor has prescribed JURNISTA<sup>®</sup> to help control moderate to severe pain requiring the continuous around-the-clock use of an opioid analgesic preparation for several days or more.

**What it does:**

After you take JURNISTA<sup>®</sup>, the medicine in JURNISTA<sup>®</sup> is gradually released from the tablet and absorbed throughout the intestinal tract (gut) for approximately 24 hours to help you manage your pain.

The tablets are coated with a special membrane, which does not dissolve and may pass through your body unchanged. Do not be alarmed if you notice what appears to be the JURNISTA<sup>®</sup> tablet in your stools, as it is simply the shell.

You should only take JURNISTA<sup>®</sup> once a day to manage your pain.

While most patients obtain adequate pain relief with JURNISTA<sup>®</sup>, your pain may vary and occasionally break through. This is not unusual. If this occurs, your doctor may prescribe additional pain medication.

It is important to let your doctor know whether or not your pain is under control. If you frequently need additional short-acting pain medication, or if pain is waking you at night, you may need a change in your JURNISTA<sup>®</sup> dose.

**If you continue to have pain, call your doctor.**

Always follow your doctor's instructions carefully and do not change or stop your JURNISTA<sup>®</sup> medication without first consulting with your doctor.

**When it should not be used:**

JURNISTA<sup>®</sup> should not be used:

- if you are allergic (hypersensitive) to hydromorphone hydrochloride or any of the other ingredients of JURNISTA<sup>®</sup> (see **What the nonmedicinal ingredients are**)
- if your pain can be controlled by occasional use of painkillers
- if you have acute or severe bronchial asthma
- if you have difficulty in breathing
- if you have been diagnosed with serious narrowing of the intestine or intestinal blockage, such as "paralytic ileus"
- if you have had surgery or medical conditions which may have left you with narrowing or "blind loops" in your intestine
- if you get sudden severe pain in your abdomen and the cause has not been diagnosed

- if you suffer from alcoholism or have convulsions
- if you are pregnant, or in labour or are breast-feeding
- if you have been diagnosed with rare hereditary diseases of galactose intolerance or glucose-galactose malabsorption

**What the medicinal ingredient is:**  
hydromorphone hydrochloride

**What the nonmedicinal ingredients are:**  
butyl hydroxytoluene , cellulose acetate, glycerol triacetate, iron oxide black , ferric oxide red (4 mg and 8 mg only), ferric oxide yellow (4 mg, 16 mg, and 32 mg only), hypromellose, lactose anhydrous, lactose monohydrate, macrogol, magnesium stearate, polyethylene oxide, povidone, propylene glycol, sodium chloride and titanium dioxide

JURNISTA<sup>®</sup> may contain traces of sodium metabisulfite.

**What dosage forms it comes in:**  
JURNISTA<sup>®</sup> is available as 4 mg, 8 mg, 16 mg, and 32 mg prolonged-release tablets in hard non-dissolvable shells.

## WARNINGS AND PRECAUTIONS

BEFORE you use JURNISTA<sup>®</sup> talk to your doctor or pharmacist if:

- you have any other medical conditions (such as difficulty urinating or breathing or problems with your heart, lungs, brain, liver, hormones, or kidney)
- you have any intestinal disease, including obstruction or inflammatory bowel disease, pancreatitis, or other biliary tract disease
- you are pregnant or plan to become pregnant, or are breast-feeding
- you are taking any other medications (see **INTERACTIONS WITH THIS MEDICATION**)
- you have ever had an allergic reaction to any other medication
- you have a head injury or brain tumour
- you have a history of drug abuse
- you have chronic and severe constipation
- you suffer from alcoholism

This will help your doctor decide whether you should take JURNISTA<sup>®</sup> and what extra care should be taken during its use.

Do not drive a car or operate machinery until you are sure that taking JURNISTA<sup>®</sup> does not make you drowsy.

## INTERACTIONS WITH THIS MEDICATION

It is extremely important to avoid medications such as tranquilizers and sleeping pills when you are using JURNISTA<sup>®</sup>, since their combined effect may cause drowsiness, depressed breathing, low blood pressure and possibly coma.

JURNISTA<sup>®</sup> can make people drowsy. If you drink alcohol when you are taking JURNISTA<sup>®</sup>, it might make you more drowsy than usual. Do not drink alcohol while you are taking JURNISTA<sup>®</sup>.

To avoid any potential drug interactions, be sure to inform your doctor before taking any other medications while you are using JURNISTA<sup>®</sup>, including:

- monoamine (MAO) inhibitors (e.g. phenelzine sulfate, tranylcypromine sulfate, moclobemide or selegiline)
- over-the-counter medications that may cause drowsiness (e.g. antihistamines)
- muscle relaxants
- anesthetics
- sedatives or hypnotics
- phenothiazines
- other opioid pain medication

## PROPER USE OF THIS MEDICATION

### **Usual dose:**

Take JURNISTA<sup>®</sup> once a day as directed by your doctor. JURNISTA<sup>®</sup> tablets should be taken whole at approximately the same time each day with a glass of water. JURNISTA<sup>®</sup> has a hard, non-dissolvable shell. Do not be alarmed if you notice what appears to be the JURNISTA<sup>®</sup> tablet in your stools, as it is simply the shell. Never chew, divide, or crush JURNISTA<sup>®</sup> tablets. If you do, there is a danger you could overdose because the medicine will be released into your body too quickly.

JURNISTA<sup>®</sup> tablets can be taken with or without food.

### **Overdose:**

**The most important sign of overdose is suppressed breathing. If a person is breathing abnormally slowly or weakly while on JURNISTA<sup>®</sup>, seek immediate medical emergency treatment. Meanwhile, keep the person awake by talking or by shaking him/her every now and then.**

Other signs of hydromorphone overdose may include tiredness, extreme sleepiness or sedation; inability to think, talk or walk normally; and feeling faint, dizzy or confused.

### **Missed dose:**

Do not take extra tablets or a double dose to make up for forgotten tablets. Contact your doctor for advice on what to do, if you forget to take your dose.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, JURNISTA<sup>®</sup> may cause unwanted effects. Most unwanted effects appear during the first month of treatment.

The most frequently reported unwanted effects were constipation, nausea, vomiting, somnolence, headache, and dizziness.

Opioid withdrawal symptoms such as nausea, vomiting, diarrhea, anxiety and shivering are possible after converting from your previous opioid analgesic to JURNISTA<sup>®</sup>, or converting from JURNISTA<sup>®</sup> to another opioid. Contact your doctor if you experience these symptoms when switching to or from JURNISTA<sup>®</sup>.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical emergency treatment
		Only if severe	In all cases	
Common	constipation, dizziness, headache, nausea, somnolence, vomiting	✓		
Uncommon	anxiety and shivering		✓	
	breathing abnormally slowly or weakly, extreme sleepiness or sedation, confused, inability to walk normally			✓
	abdominal pain	✓		

*This is not a complete list of side effects. For any unexpected effects while taking JURNISTA<sup>®</sup>, contact your doctor or pharmacist.*

## HOW TO STORE IT

**Keep JURNISTA<sup>®</sup> out of sight and reach of children.**  
Store JURNISTA<sup>®</sup> between 15 and 25°C.

## REPORTING SUSPECTED SIDE EFFECTS

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways.**

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available in the MedEffect<sup>™</sup> Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

**NOTE:** *Should you require information related to the management of the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at: <http://www.janssen.ca> or by contacting the sponsor, Janssen Inc., at: 1-800-567-3331

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