
AUSTRALIAN PRODUCT INFORMATION

JURNISTA[®]

HYDROMORPHONE HYDROCHLORIDE

PROLONGED-RELEASE TABLETS

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, JURNISTA should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see section **4.4 Special Warnings and Precautions for Use**).

Hazardous and harmful use

JURNISTA poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see section **4.4. Special Warnings and Precautions for Use**).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of JURNISTA. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see section **4.4 Special Warnings and Precautions for Use**).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking JURNISTA.

1. NAME OF THE MEDICINE

Hydromorphone hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect: Lactose

For a full list of excipients, see section **6.1 List of excipients**.

3. PHARMACEUTICAL FORM

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

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

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

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

JURNISTA is indicated for the management of severe pain where:

- other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain, and
- the pain is opioid-responsive, and
- requires daily, continuous, long-term treatment.

JURNISTA is not indicated for use in chronic non-cancer pain other than in exceptional circumstances.

JURNISTA is not indicated as an as-needed (PRN) analgesia.

Not for use in opioid naïve patients.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

The lowest effective dose should be used for the shortest period of time (see **Discontinuation of therapy** below)

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

Patients should be instructed to swallow JURNISTA prolonged-release tablet whole with a glass of water, at approximately the same time each day, and never to chew, divide, or crush it. JURNISTA may be taken with or without food.

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

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

Opioid-tolerant patients (currently receiving opioids regularly)

In patients currently taking opioid analgesics regularly, the starting dose of JURNISTA should be based on the prior daily opioid dose (the total opioid daily dose in milligrams regardless of the dosage form), using standard equi-analgesic ratios. For opioids other than morphine, first estimate the equivalent total daily dose of morphine, then use the conversion table below (Table 1) to determine the equivalent total daily dose of JURNISTA.

Table 1: Conversion Table: Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of JURNISTA

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

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

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

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

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

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

Supplemental Rescue Medication

In addition to once-daily JURNISTA therapy, supplemental breakthrough pain medication in the form of immediate release preparations (e.g., immediate release hydromorphone or immediate release morphine) could be made available to all patients with chronic pain. For conversion, the conversion table should be used. Individual supplemental doses of immediate release hydromorphone or immediate release morphine should generally not exceed 10% to 25% of the 24 hour JURNISTA dose (see Table 2 below).

Table 2: Recommended Starting Dose for Supplemental Rescue Medication

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

Individualisation of dosage and maintenance of therapy:

After initiation of therapy with JURNISTA, dose adjustments may be necessary to obtain the patient's best balance between pain relief and opioid-related adverse reactions. If the pain increases in severity or analgesia is inadequate, a gradual increase in dosage may be required. In order to allow the effects of the dose change to stabilise, the dosage should be increased no more frequently than every fourth dose (for example, if the first dose is given on a Monday, the dosage could be increased no earlier than the fourth dose, on Thursday). As a guideline, dosage increases of 25%-100% of the current daily dose of JURNISTA should be considered for each titration step.

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

Use in children and adolescents

JURNISTA is not recommended for use in children and adolescents below the age of 18 due to insufficient data on safety and efficacy. (see section **4.3 CONTRAINDICATIONS**)

Use in the elderly

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

Use in patients with renal and hepatic impairment

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

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

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

Discontinuation of therapy

In patients who are physically dependent on opioids and receiving daily administration of hydromorphone, abrupt discontinuation of treatment with JURNISTA will result in symptoms of withdrawal syndrome. There have been reports that rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms and uncontrolled pain (see section **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Ceasing Opioids**). Therefore, if discontinuation of therapy with JURNISTA is indicated in patients, the dose of JURNISTA should be reduced by no more than 10 percent to 25 percent every 2 to 4 weeks until the lowest possible dose is reached, at which time therapy may be safely discontinued. If symptoms of withdrawal appear, tapering should be stopped. The dose should be slightly increased until the signs and

symptoms of opioid withdrawal disappear. Tapering should then begin again but with longer periods of time between each JURNISTA dose reduction, or before converting to an equianalgesic dose of another opioid to continue tapering.

4.3 CONTRAINDICATIONS

JURNISTA is contraindicated in:

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypotension

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

Paralytic ileus

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

Chordotomy

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

Hazardous and harmful use

JURNISTA contains the opioid hydromorphone and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed JURNISTA at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed JURNISTA.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section **6.4 SPECIAL PRECAUTIONS FOR STORAGE** and section **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share JURNISTA with anyone else.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of JURNISTA but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail or debilitated patients, in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma) and in patients with hepatic and renal impairment (see subsections **Use in hepatic impairment**, **Use in renal impairment** of this section). Opioids should be used with caution and with close monitoring in these patients (see section **4.2 DOSE AND METHOD OF ADMINISTRATION**). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section **4.3 CONTRAINDICATIONS**).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see section **4.2 DOSE AND METHOD OF ADMINISTRATION**) together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

Severe pain antagonises the respiratory depressant effects of opioids. However, should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for regional anaesthetic procedures or other interruptions of pain transmission pathways should not receive JURNISTA within 24 hours of the procedure but should be provided with immediate release opioid analgesics.

Opioids can cause sleep-related breathing disorders such as sleep apnoea syndromes (including central sleep apnoea [CSA]) and hypoxia (including sleep-related hypoxia) (see section **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnoea, or a worsening of an existing sleep apnoea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see section **4.2 DOSE AND METHOD OF ADMINISTRATION, Discontinuation of therapy**).

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of JURNISTA with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible.

If a decision is made to prescribe JURNISTA concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms.

Since alcohol increases the sedative effect of hydromorphone concomitant use of JURNISTA and alcohol should be avoided (see section **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, "Alcohol"**). Patients and their

caregivers should also be informed of the potential harms of consuming alcohol while taking JURNISTA.

Head injury and increased intracranial pressure

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

Gastrointestinal tract and other smooth muscle

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

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

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

The JURNISTA prolonged-release tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract. There have been very rare reports of obstructive symptoms in patients with known strictures in association with ingestion of medicinal products in non-deformable controlled-release formulations (see section **4.3 CONTRAINDICATIONS**).

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

Use in hepatic impairment

Moderate hepatic impairment results in a four-fold increase in hydromorphone plasma levels. Patients with moderate hepatic insufficiency should be started on a reduced dose and closely monitored during dose titration (see section **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Use in renal impairment

Moderate and severe renal impairment results in two-fold and four-fold increases in hydromorphone bioavailability respectively. Patients with moderate renal insufficiency should be started on a reduced dose and closely monitored during dose titration. In patients with severe renal insufficiency an increased dosing interval should also be considered and these patients should, in addition, be monitored during maintenance therapy for development of opioid-related adverse reactions. (see section **4.2 DOSE AND METHOD OF ADMINISTRATION**)

Use in the elderly

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

Paediatric use

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

Effects on laboratory tests

No data available.

Use in special risk patients

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

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see **Hazardous and harmful use**, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse.

Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see **Ceasing Opioids**).

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing JURNISTA in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see **Ceasing opioids** and section **4.2 DOSE AND METHOD OF ADMINISTRATION**). There have been reports that rapid tapering of JURNISTA in a patient physically dependent on opioids may lead to serious withdrawal symptoms and uncontrolled pain. (see section **4.2 DOSE AND METHOD OF ADMINISTRATION – Discontinuation of therapy**)

JURNISTA should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of opioid tolerance and psychological dependence observed in these patient populations. Intravenous administration of some non-active components of JURNISTA to animals has been shown to cause anaemia, degeneration and necrosis of myocardial cells and renal tubular epithelial cells and death. With abuse by parenteral routes, the tablet excipients may cause lethal complications. **JURNISTA must not be administered by a parenteral route.** Oral use of these excipients was not associated with negative findings. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

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

Accidental ingestion/exposure

Accidental ingestion or exposure of JURNISTA, especially by children, can result in a fatal overdose of hydromorphone. Patients and their caregivers should be given information on safe storage and disposal of unused JURNISTA (see section **6.4 SPECIAL PRECAUTIONS FOR STORAGE** and section **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Opioid induced hyperalgesia is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. Hyperalgesia may manifest as an

unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. Hyperalgesia should not be confused with tolerance. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain (see **Tolerance, dependence and withdrawal**). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see **Tolerance, dependence and withdrawal**). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see section **4.2 DOSE AND METHOD OF ADMINISTRATION**). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Lactose

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

Sulfite allergy

JURNISTA may contain 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Based on hydromorphone's pharmacodynamic and pharmacokinetic properties, the following interactions have been identified

| Central Nervous System (CNS) depressants, including alcohol and some illegal drugs | |
|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Clinical Impact</i> | Due to additive pharmacodynamic effects, the concomitant use of JURNISTA with central nervous system depressants may disproportionately increase the CNS depressant effects and respiratory depression. Additionally, hypotension and profound sedation, coma or death may occur. |
| <i>Intervention</i> | When this combination is indicated, the dose of one or both |

| | |
|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | agents should be reduced. |
| <i>Examples</i> | Other central nervous system depressants, including benzodiazepines and other hypnotics/sedatives, opioid analgesics, gabapentinoids, antihistamines, tricyclic antidepressants, centrally active anti-emetics, general anesthetics, antipsychotics, cannabis and alcohol and some illegal drugs. |
| Monoamine Oxidase Inhibitors (MAOI) | |
| <i>Clinical Impact</i> | Due to additive pharmacodynamic effects, Monoamine oxidase inhibitors (MAOIs) may cause central nervous system excitation or depression, hypotension or hypertension if co-administered with opioids. |
| <i>Intervention</i> | JURNISTA is not intended for patients taking MAOIs or within 14 days of stopping such treatment. |
| Morphine agonists/antagonists | |
| <i>Clinical Impact</i> | The concomitant use of hydromorphone with morphine agonists/antagonists could lead to a reduction of the analgesic effect by competitive blocking of receptors, thus leading to risk of withdrawal symptoms. |
| <i>Intervention</i> | The combination of hydromorphone and morphine agonists/antagonists is not recommended. |
| <i>Examples</i> | buprenorphine, nalbuphine, pentazocine |
| Muscle Relaxants | |
| <i>Clinical Impact</i> | JURNISTA, like other opioids, may enhance the neuromuscular blocking action of muscle relaxants and cause an increased degree of respiratory depression. |

Alcohol

The concomitant use of alcohol should be avoided. Alcohol increases the sedative effect of hydromorphone. In addition, peak hydromorphone concentrations are increased when JURNISTA is taken with alcohol (mean 30-35%). Due to the OROS[®] technology in JURNISTA, the prolonged-release properties of JURNISTA are maintained in the presence of alcohol (see section 5.2 PHARMACOKINETIC PROPERTIES).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In an oral fertility study in rats, a slight but statistically significant reduction in implantations was observed at a maternotoxic dose of 6.25 mg/kg/day, associated with estimated hydromorphone exposure (plasma AUC) slightly less than steady-state human exposure with a dose of 64 mg. Male fertility was unaffected up to this dose. A low incidence of testicular tubular atrophy was documented in a repeated dose study in rats at a dose of 14 mg/kg/day (relative exposure 9.2 times the human exposure at 64 mg, based on AUC). The effects of JURNISTA on human fertility are unknown.

Use in pregnancy

Category C.

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

Hydromorphone crosses the placental barrier in experimental animals. No malformations were observed following oral administration of hydromorphone to rats and rabbits during the period of organogenesis at respective doses up to 6.25 and 25 mg/kg/day, associated with maternotoxicity and systemic exposures (plasma AUC) slightly less than steady-state clinical exposure at a dose of 64 mg. In rats, an increased incidence of runts was observed at 6.25 mg/kg/day (no-effect dose 3.13 mg/kg/day), but no embryotoxicity was seen in the rabbits. The potential teratogenic risk for humans from use of hydromorphone and other opioids during pregnancy is unknown.

Use in lactation

No clinical data are available on the use of hydromorphone during lactation. Low concentrations of hydromorphone and other opioid analgesics have been detected in human milk in clinical studies. Preclinical studies have shown that following a single oral dose of [¹⁴C] hydromorphone to lactating rats, less than 1% of radiolabelled material was excreted into milk in 24 hours after dosing. Neonatal viability and development were also adversely affected in rats at maternal oral doses of 3.13 mg/kg/day and higher from early gestation to weaning (AUC exposure less than half the human exposure at 64 mg). JURNISTA should not be used during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Studies Data

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

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

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

Respiratory depression may be more likely in certain subgroups of patients (see section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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

Very Common (≥ 1/10)

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

Common ($\geq 1/100$ to $< 1/10$)

| | |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Metabolism & nutrition disorders: | Anorexia, weight decrease, dehydration, decreased appetite |
| Psychiatric disorders: | Insomnia, anxiety, confusional state, nervousness, abnormal dreams, depression, mood alterations, restlessness, hallucination |
| Nervous system disorders: | Memory impairment, hypoaesthesia, paraesthesia, tremor or involuntary muscle contractions, sedation, disturbance in attention, dysgeusia |
| Eye disorders: | Visual disorders such as blurred vision |
| Ear & labyrinth disorders: | Vertigo |
| Cardiac disorders: | Tachycardia |
| Vascular disorders: | Hypotension, flushing, hypertension |
| Respiratory, thoracic & mediastinal disorders: | Dyspnoea |
| Gastrointestinal disorders: | Dry mouth, diarrhoea, abdominal pain, dyspepsia, dysphagia, flatulence, oesophageal reflux aggravated |
| Skin & subcutaneous tissue disorders: | Hyperhidrosis, pruritus, rash |
| Musculoskeletal & connective tissue disorders: | Muscle spasms, back pain, arthralgia, pain in extremity |
| Renal & urinary disorders: | Urinary retention, dysuria, micturition urgency |
| General disorders & administration site conditions: | Oedema, drug withdrawal syndrome, pyrexia, pain, chest discomfort, chills |
| Investigations: | Weight decreased |
| Injury, poisoning & procedural complications: | Fall, contusion |

Uncommon ($\geq 1/1000$ to $< 1/100$)

| | |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Infections & infestations: | Gastroenteritis, diverticulitis |
| Metabolism & nutrition disorders: | Increased appetite, fluid retention, hyperuricaemia |
| Psychiatric disorders: | Libido decreased, panic attack, paranoia, aggression, crying, listless, dysphoria, euphoric mood, sleep disorder |
| Nervous system disorders: | Myoclonus, coordination abnormal, dyskinesia, syncope, dysarthria, balance disorder, depressed level of consciousness, hyperaesthesia, encephalopathy, cognitive disorder, psychomotor hyperactivity, fits/convulsions |
| Eye disorders: | Miosis, diplopia, dry eye |
| Ear & labyrinth disorders: | Tinnitus |
| Cardiac disorders: | Palpitations, extrasystoles |
| Respiratory, thoracic & Mediastinal disorders: | Respiratory distress, rhinorrhoea, hypoxia, bronchospasm, hyperventilation, sneezing |
| Gastrointestinal disorders: | Abdominal distension, haemorrhoids, haematochezia, abnormal faeces, intestinal obstruction, diverticulum, eructation, gastrointestinal motility disorder, large intestine perforation, dysphagia |
| Musculoskeletal & connective tissue disorders: | Myalgia |
| Renal & urinary disorders: | Urinary hesitation, pollakiuria |
| Reproductive system & breast disorders: | Erectile dysfunction/impotence, sexual dysfunction |
| General disorders & administration site conditions: | Feeling abnormal, malaise, difficulty in walking, feeling jittery, hangover, influenza-like illness, gait disturbance |

| | |
|-----------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Investigations: | Oxygen saturation decreased, blood potassium decreased, hepatic enzyme increased, blood amylase increase |
| Injury, poisoning & procedural Complications: | Overdose |

Rare ($\geq 1/10,000$ to $<1/1000$)

| | |
|-----------------------------------------------------|-----------------------------------------------------------------------------------------|
| Endocrine disorders: | Hypogonadism |
| Nervous system disorders: | Hyperreflexia |
| Cardiac disorders: | Bradycardia |
| Respiratory, thoracic & Mediastinal disorders: | Respiratory depression |
| Gastrointestinal disorders: | Anal fissure, bezoar, duodenitis, ileus, impaired gastric emptying, painful defaecation |
| Hepatobiliary disorders: | Biliary colic |
| Skin & subcutaneous tissue disorders: | Reddening of face/erythema, skin burning sensation |
| General disorders & administration site conditions: | Feeling drunk, feeling of body temperature changes, hypothermia |
| Investigations: | Blood testosterone decreased, body temperature decreased |

Post-marketing Data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience (Table 3). In each table, the frequencies are provided according to the following convention:

| | |
|-------------|-------------------------------------------|
| Very common | $\geq 1/10$ |
| Common | $\geq 1/100$ and $< 1/10$ |
| Uncommon | $\geq 1/1000$ and $< 1/100$ |
| Rare | $\geq 1/10000$ and $< 1/1000$ |
| Very rare | $< 1/10000$, including isolated reports. |

Table 3. Adverse Reactions Identified During Post-marketing Experience with JURNISTA by Frequency Category Estimated from Spontaneous Reporting Rates

| System Organ Class | Adverse Reaction |
|---------------------------------|-----------------------|
| Immune System Disorders | |
| <i>Very rare</i> | Hypersensitivity |
| Skin and subcutaneous disorders | |
| <i>Very rare</i> | Angioedema, Urticaria |
| Nervous System Disorders | |
| <i>Very rare</i> | Sleep apnoea syndrome |

Other adverse effects of hydromorphone include:

| | |
|------------------------------------------------------|----------|
| General disorders and administration site conditions | |
| Uncommon | Fatigue |
| Nervous system disorders | |
| Rare | Lethargy |

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

In the treatment of overdosage, primary attention should be given to the reestablishment of adequate respiratory exchange keeping the airway open and instituting assisted or controlled ventilation.

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

In cases of severe overdosage, specific antidotes such as naloxone should be used to manage respiratory depression (see prescribing information for the specific opioid antagonists for details of proper use). The effect of naloxone is relatively short; therefore, the patient should be carefully monitored until respiration has stabilised. JURNISTA will release hydromorphone for approximately 24 hours. This should be taken into account in determining the treatment. Opioid antagonists should not be given in the absence of clinically significant respiratory depression, or circulatory depression because of opioids. Opioid antagonists should be administered with caution to patients suspected to be physically dependent on hydromorphone, since rapid reversal of an opioid, including hydromorphone, may precipitate symptoms of withdrawal.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

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

5.1 PHARMACODYNAMIC PROPERTIES

MECHANISM OF ACTION

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

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

CLINICAL TRIALS

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

The four controlled studies were conducted in patients with cancer pain (Study DO-118), patients with osteoarthritis (OA) pain (Studies DO-132 and M03-644), and patients with non-malignant or cancer pain (Study DO-119). Three of the four controlled studies evaluated JURNISTA against an active control: morphine sulfate SR (DO-118), OxyContin® (DO-132), and IR hydromorphone (DO-119). Study M03-644 was placebo-controlled.

The three active-controlled studies included a titration phase where patients had their dose of JURNISTA adjusted to obtain the optimum balance of benefits and side effects. In Study M03-644, patients were assigned a fixed dose of JURNISTA and no dose adjustments were allowed.

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

Study Demographics and Trial Design

Table 4: Summary of Patient Demographics for JURNISTA Clinical Trials

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

Study Results

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

evening (PM) in the SR phase, where patients treated with JURNISTA had a lower pain intensity PM mean adjusted score (2.6) than patients treated with morphine SR (3.4), $p=0.0372$, no statistically significant differences were observed in any other secondary efficacy measures, such as the use of breakthrough pain medication.

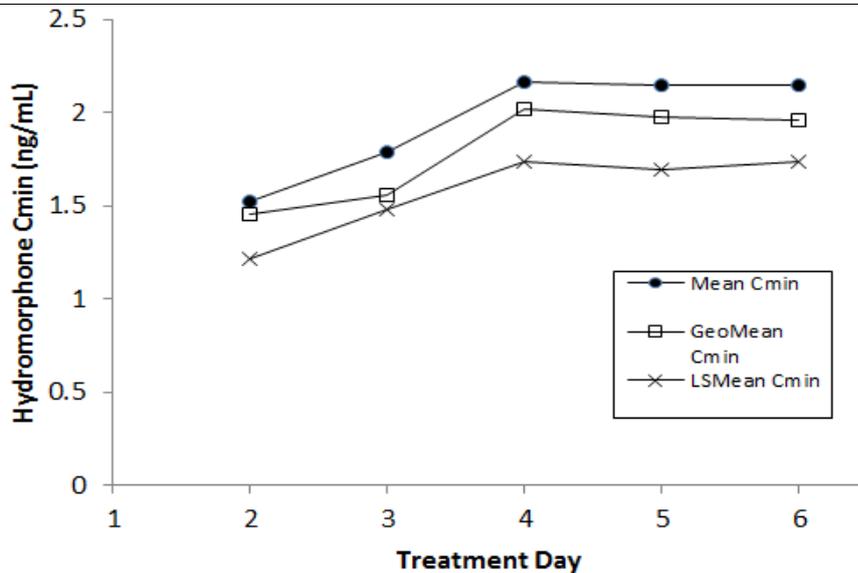
Study DO-132 was a multicentre, open-label, randomised, repeated-dose, 2-arm, parallel-group study characterising the efficacy and safety of JURNISTA once daily and extended-release oxycodone b.i.d. in patients with chronic osteoarthritis (OA) of the knee and hip who were on chronic non-steroidal anti-inflammatory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

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

5.2 PHARMACOKINETIC PROPERTIES

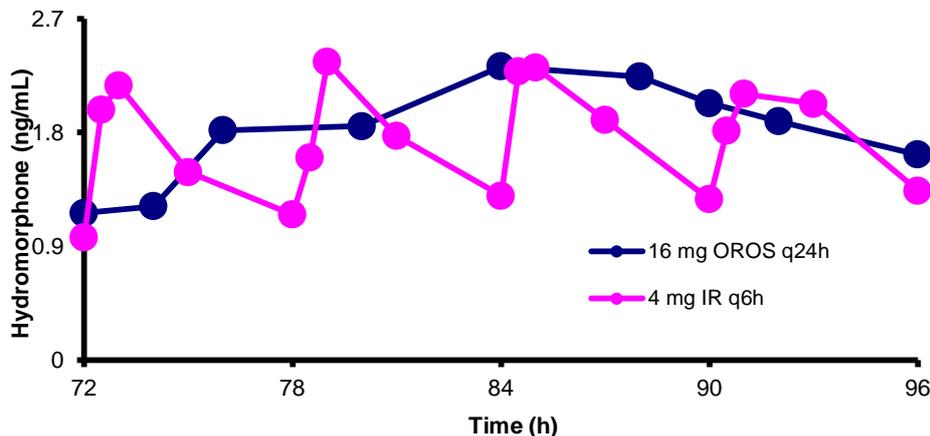
Following a single oral dose of JURNISTA prolonged-release tablets, plasma concentrations reach a broad, relatively plateau region within 6 to 8 hours and remain in this plateau region until approximately 24 hours post-dose; the mean T_{max} values were approximately 13 to 16 hours. This demonstrates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

Figure 1: Study 42801-PAI-1009. Trough hydromorphone concentrations in plasma during repeated dosing.



Steady state plasma concentrations are approximately twice those observed following the first dose, and steady state is reached by the fourth dose of JURNISTA. No time-dependent change in pharmacokinetics was seen with multiple dosing. At steady state, JURNISTA given once daily maintained hydromorphone plasma concentrations within the same concentration range as the immediate-release tablet given 4 times daily at the same total daily dose and diminishes the periodic fluctuations in plasma levels seen with the immediate-release tablet. The degree of fluctuation in plasma concentration at steady state during a 24-hour period [calculated as $(C_{\max(ss)} - C_{\min(ss)}) / C_{\text{avg}(ss)} \times 100\%$] was lower with JURNISTA (83%) as compared to the overall fluctuations of the immediate-release tablet (147%) (see **Figure 2**). At steady state, hydromorphone AUC for JURNISTA is equivalent to that observed for the immediate-release tablet.

Figure 2. Steady-State Plasma Concentration Profile (n = 18 naltrexone blocked healthy subjects)



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

The effect of age on the pharmacokinetics of hydromorphone immediate-release resulted in a 14% decrease in C_{\max} and a modest increase (11%) in AUC in the elderly compared to the young. No difference in T_{\max} was observed. These effects are considered unlikely to be

clinically relevant. Greater sensitivity of older individuals cannot be excluded. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

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

In studies that used single oral dosing with conventional immediate-release tablets, hepatic impairment reduces the first-pass metabolism of hydromorphone such that four-fold higher plasma levels of hydromorphone are seen in subjects with moderate hepatic dysfunction. Renal impairment affected the pharmacokinetics of hydromorphone and its metabolite, hydromorphone 3-glucuronide, following administration of a single oral dose of the immediate-release tablet. The effects of renal impairment on hydromorphone pharmacokinetics were two-fold and four-fold increases in hydromorphone bioavailability in moderate and severe renal impairment, respectively. There were also substantial changes in hydromorphone 3-glucuronide elimination kinetics for the severe renal impairment group, although haemodialysis was effective at reducing plasma levels of both hydromorphone and metabolites. (see section **4.2 DOSE AND METHOD OF ADMINISTRATION**).

In a study evaluating hydromorphone absorption from JURNISTA when taken with 240 mL of 4%, 20% and 40% alcohol, C_{max} increased on average by 17, 31, and 28% respectively in the fasting state and was less affected in the fed state with increases of 14, 14, and 10% respectively. Median T_{max} (fasted and fed) with 4, 20 and 40% alcohol was 12 to 16 hour and with no alcohol was 16 hour. No effect was seen on AUC values both in the fed and fasted state. Concomitant use of alcohol should be avoided (see section **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Long-term studies of hydromorphone showed no evidence of any carcinogenic effects after daily oral dosing for two years at doses of up to 15 mg/kg/day in mice and male rats and 25 mg/kg/day in female rats, associated with steady state plasma exposure (AUC) of about 0.5-times (mice) and greater than 3-times (rats) the steady-state human exposure at a dose of 64 mg. Malignant hibernomas occurred in the brown adipose tissue of female rats that received 75 mg/kg/day hydromorphone, which was associated with exposure more than 20-times that expected in patients receiving 64 mg JURNISTA. This finding is unlikely to be clinically relevant, although this has not been established.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

JURNISTA prolonged-release tablets contain the inactive ingredients:

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

Colour overcoat: lactose monohydrate, hypromellose, titanium dioxide (E171), glycerol triacetate and iron oxide red (E172) (for the 4 mg and 8 mg strength)/iron oxide black (for the

4 mg strength only)/iron oxide yellow (for the 4 mg and 16 mg strength)/indigo carmine lake (E132) (for the 64 mg strength).

Clear overcoat: hypromellose and macrogol 400.

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

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store JURNISTA securely, in a location not accessible by others.

6.5 NATURE AND CONTENTS OF CONTAINER

All strengths of JURNISTA prolonged-release tablets are available in PVC/PCTFE(Aclar)/Al blister packs of 10 and 14 tablets.

Blister packs of 7, 20, 28, 30, 35, 40, 50, 60 and 100 tablets are currently not-marketed.

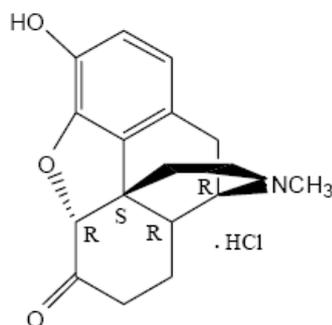
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Hydromorphone hydrochloride has four asymmetric carbon atoms (C₅, C₉, C₁₃ and C₁₄), with a specific rotation (20°C, 589 nm) of -136.5° to -138.5°. No cis-trans isomerism or threo-erythro isomerism was detected. No other isomers are known.

Chemical structure



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

C₁₇H₁₉NO₃.HCl MW: 321.8

CAS number

71-68-1

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

7. MEDICINE SCHEDULE (POISONS STANDARD)

S8 – Controlled Drug.

8. SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Road
Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334

NZ Office: Auckland, New Zealand
Telephone: 0800 800 806

9. DATE OF FIRST APPROVAL

15 June 2010

10. DATE OF REVISION

12 October 2020

OROS® formulation is a trademark of ALZA Corporation

SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 4.4 | <ul style="list-style-type: none">• Updates to Hyperalgesia section – added further explanation and examples of hyperalgesia |