1. PRODUCT NAME

RA-MORPH®

Morphine Hydrochloride BP Solution 1, 2, 5, and 10 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Morphine hydrochloride is 7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol hydrochloride trihydrate (molecular weight 375.8). It is a white, crystalline powder or colourless, silky crystals. It is soluble 1:21 in water and 1:10 in boiling alcohol. It is practically insoluble in chloroform or ether.

RA-MORPH contains Morphine Hydrochloride BP 1, 2, 5, and 10 mg/mL in a sugar and alcohol free vehicle.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

RA-MORPH solutions are clear colourless or pale yellow solutions.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Morphine is an analgesic used for the symptomatic relief of moderate to severe pain, especially that associated with neoplastic disease, myocardial infarction, and surgery. Morphine is indicated in adults and children aged 1 year and above. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage must be titrated to the patient's needs because of the wide inter-individual variability in plasma concentration required to achieve analgesia.

The usual adult dosage is 5-20 mg (2.5-10 mL of the 2 mg/mL mixture) every 4 hours. The initial dose will depend largely on the patient’s previous treatment and should be the lowest compatible with pain control. Treatment should start at a dosage of 5 mg every 4 hours, with further increments as required. With repeat administration, tolerance may develop and the dose may need to be increased gradually in order to control the pain.

Dosage should be lower in elderly patients, those with respiratory, hepatic or renal impairment and in patients receiving CNS depressants.

Dosage in children should be adjusted according to body weight, 0.1-0.2 mg/kg every 4 hours.

4.3 CONTRAINDICATIONS

Morphine is contraindicated:

- in patients hypersensitive to narcotics
- in children under one year of age including premature infants or during labour or delivery of premature infants
- following biliary tract surgery or surgical anastomosis
• in patients with paralytic ileus
• in patients who are taking, or have taken MAO inhibitors, within the previous fourteen days.
• in respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of RA-MORPH with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when RA-MORPH is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

Drug Dependence

Narcotic analgesics have abuse potential, and should only be used with caution in patients with a history of substance abuse and alcohol abuse. Psychological and physical dependence, and tolerance may occur with repeated dosing. Except in patients with terminal conditions, morphine should be restricted to short-term administration for the relief of severe pain not responding to non-narcotic analgesics.

Abrupt withdrawal of morphine in those physically dependent may precipitate withdrawal syndrome, including convulsions. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

Abuse of Oral Dosage Forms

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

Nervous System

Use with extreme caution in patients with severe CNS depression, head injury and increased cerebrospinal or intracranial pressure. Respiratory depressant effects and ability to increase cerebrospinal fluid pressure may be exaggerated, and the clinical course obscured.

Morphine should be used with caution in patients with a brain tumour.
Seizures may result from high doses. Morphine may lower the seizure threshold in patients with a history of seizures. Patients with known seizure disorders should be carefully observed, especially when doses are increased in response to tolerance.

Morphine should be used with caution in patients with convulsive states such as status epilepticus.

The development of serotonin syndrome (SS), which is potentially life-threatening, has been reported with opioid use, including with morphine. These reports generally occurred when morphine was used concomitantly with serotonergic drugs (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION). Signs of SS may include clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia and temperature elevation.

Respiratory

Therapeutic doses of narcotics may decrease respiratory drive and increase airway resistance to the point of apnoea in patients with acute bronchial asthma, chronic obstructive pulmonary disease or cor pulmonale, or those with a substantially decreased pulmonary reserve or respiratory depression. Resuscitative equipment and narcotic antagonists must be readily available.

Cardiac

Morphine should be used with caution in patients with heart failure secondary to chronic pulmonary disease or cardiac arrhythmias.

Morphine should be used with caution in patients with supraventricular tachycardia since morphine can increase the ventricular response rate.

Morphine should be used with caution in patients with low blood pressure and those at risk for developing hypotension.

Endocrine

Cases of adrenal insufficiency have been reported with opioid use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure.

General

Morphine should be used with caution in patients with acute alcoholism or delirium tremens.

Morphine should be used with caution pre-operatively or within the first 24 hours, post-operatively.

Caution should be taken in prescribing morphine for patients with severely impaired pulmonary, hepatic or renal function and those with hypothyroidism, pancreatitis, biliary tract disorders, adrenocortical insufficiency, prostatic hypertrophy and urethral stricture.

Hepatobiliary

Morphine should be used with caution in patients with tetanus due to stimulatory effects on the spinal cord or strychnine poisoning.

Reproductive

Prolonged use of opioids may result in impairment of reproductive function, including fertility and sexual dysfunction in both sexes and irregular menses in women.

Elderly

Morphine should be administered with extreme caution in aged or debilitated patients. Patients with reduced circulating volume, impaired myocardial function or who are receiving sympatholytic drugs should be carefully observed for orthostatic hypotension.

Gastrointestinal

Morphine may obscure the diagnosis and clinical course in patients with acute abdominal conditions, and should be used with caution in those with obstructive bowel disorders, or ulcerative colitis. Due
to the spasmogenic properties of morphine in the biliary tract and sphincter of Oddi, it should be used only when necessary, and with caution in biliary colic, operations on the biliary tract and acute pancreatitis.

Gastrointestinal Motility

Decreased gastric emptying associated with morphine may be expected to increase the risks of aspiration either associated with morphine induced CNS depression/coma, or during or after general anaesthesia. As with all oral morphine preparations, RA-MORPH oral solution should be used with caution post-operatively and following abdominal surgery, as morphine impairs intestinal motility and should not be used until the physician is assured of normal bowel function.

Should paralytic ileus be suspected or occur during use, RA-MORPH oral solution should be discontinued immediately.

Cordotomy

Severe pain antagonises the subjective and respiratory depressant actions of morphine. Should pain suddenly subside, these effects may rapidly manifest. Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive RA-MORPH oral solution within 24 hours of the procedure. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, should be managed with short-acting analgesic agents. If further treatment with RA-MORPH oral solution is then indicated, the dosage should be adjusted to the new post-operative requirement.

Paediatric Use

Safety and effectiveness in neonates have not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Acidifying/Alkalising Agents

The clearance of morphine may be increased by acidifying agents and decreased by alkalising agents. Morphine's actions on gastrointestinal motility may influence absorption of other drugs.

Amphetamines, Chlorpromazine and Methocarbamol

The analgesic effect of morphine is potentiated by amphetamines, chlorpromazine and methocarbamol.

CNS Depressants

CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, tranquillisers, chloral hydrate and glutethimide may enhance the depressant effects of morphine. Monoamine oxidase inhibitors (including procarbazine hydrochloride), pyrazolidone antihistamines, cimetidine, beta-blockers and alcohol may also enhance the depressant effect of morphine. The interactive effects may include respiratory depression, hypotension, profound sedation and coma.
### Benzodiazepines and other Central Nervous System (CNS) Depressants

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).</td>
</tr>
<tr>
<td>Examples</td>
<td>Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.</td>
</tr>
</tbody>
</table>

**Coumarin Derivatives**

Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

**Other Serotonergic Drugs**

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. Drugs that affect the serotonergic neurotransmitter system include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, and monoamine oxidase inhibitors (MAOIs).

**Monoamine Oxidase Inhibitors (MAOIs)**

Non-selective MAOIs intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion and significant respiratory depression, sometimes leading to coma. Morphine should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment. It is not known whether there is an interaction between the selective MAOIs (e.g. moclobemide, selegiline) and morphine, therefore caution is advised with this drug combination.

**Ritonavir**

Ritonavir may increase the activity of glucuronyl transferases, and co-administration with morphine may result in decreased morphine serum levels and possible loss of analgesic efficacy.

**Other H2 Receptor Antagonists (cimetidine and ranitidine)**

There is a report of confusion and severe respiratory depression when a patient receiving haemodialysis was administered morphine and cimetidine. In addition, confusion has also been associated with concomitant use of ranitidine and morphine. Therefore, caution is advised when administering morphine with cimetidine or ranitidine.

**Diuretics**

Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also induce acute urinary retention.

**Zidovudine**

Morphine may competitively inhibit glucuronidation of zidovudine thus reducing its clearance. Concurrent use of morphine and zidovudine should be avoided because the toxicity of either or both of these drugs may be increased.
4.6 FERTILITY, PREGNANCY AND LACTATION

Use in Pregnancy

Australian Pregnancy Categorisation C: Morphine crosses the placental barrier and its administration during labour may cause respiratory depression in the newborn infant. Morphine should therefore only be used during the last 2-3 hours before expected delivery after weighing the expected benefits for the mother against the potential risk to the foetus.

Morphine has been associated with foetal CNS defects in rodent studies. Safe use in pregnancy prior to labour has not been established in respect to possible adverse effects on foetal development. Morphine may prolong labour by reducing the strength and frequency of uterine contractions.

Infants born of mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

Use in Lactation

Morphine appears in breast milk. Morphine administration to nursing mothers is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since morphine may cause drowsiness and general impairment of co-ordination, ambulatory patients should be cautioned against driving or operating dangerous machinery.

4.8 UNDESIRABLE EFFECTS

The major hazards associated with morphine, as with other narcotic analgesics, are respiratory depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following use of morphine.

Most Common Adverse Effects Requiring Medical Attention

The most frequently observed side effects of narcotic analgesics such as morphine are sedation, nausea and vomiting, constipation and sweating.

Sedation

Most patients experience initial drowsiness partly for pharmacokinetic reasons and partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in three to five days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusional symptoms. If excessive sedation persists, the reason for it must be sought. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated in an older patient, or the patient is actually more severely ill than realised. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension particularly in elderly or debilitated patients. It can be alleviated if the patient lies down. Because of the slower clearance in patients over 50 years of age, an appropriate dose in this age group may be as low as half or less the usual dose in the younger age group.

Nausea and Vomiting

Nausea and vomiting occur frequently after single doses of narcotics or as an early unwanted effect of regular narcotic therapy. When instituting prolonged therapy for chronic pain, the routine prescription of an antiemetic should be considered. Patients taking the equivalent of a single dose of 20 mg or more of morphine usually require an antiemetic during early therapy. Small doses of prochlorperazine or haloperidol are the most frequently prescribed antiemetics. Nausea and vomiting tend to lessen in a week or so but may persist due to narcotic-induced gastric stasis. In such patients, metoclopramide is often useful.
Constipation

Practically all patients become constipated while taking narcotics on a persistent basis. Elderly or bedridden patients may become impacted. It is essential to caution patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged narcotic therapy. Dietary modification, suitable exercise and softeners, laxatives and other appropriate measures should be used as required.

Other Adverse Reactions Include

Cardiac Disorders
Supra-ventricular tachycardia, hypotension, postural hypotension, palpitations, faintness, syncope.

Nervous System Disorders
Euphoria, dysphoria, weakness, insomnia, dizziness, confusional symptoms, vertigo.
Occasionally: hallucinations, visual disturbances, headache, involuntary muscle contraction, asthenia, somnolence, thought abnormalities.
Uncommonly: malaise, mood changes, seizures, miosis, paraesthesia, agitation.

Gastrointestinal Disorders
Dry mouth, anorexia, dyspepsia, ileus, constipation, abdominal pain and cramps, taste alterations, gastrointestinal disorders, biliary tract cramps, urinary retention or hesitance.
Uncommonly: elevated hepatic enzymes.

Reproductive System and Breast Disorders
Amenorrhoea, erectile dysfunction, reduced libido or potency, hypogonadism.

Respiratory, Thoracic and Mediastinal Disorders
Respiratory depression, bronchospasm, cough decreased.

Endocrine Disorders
Uncommonly: peripheral oedema, pulmonary oedema, syndrome of inappropriate antidiuretic hormone secretion characterised by hyponatraemia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary).
Frequency not known: adrenal insufficiency.

General Disorders and Administration Site Conditions
Allergic reaction, anaphylactic and anaphylactoid reactions, drug dependence, facial flushing, pruritus, urticaria, other skin rashes, hypertonia, oedema.

Withdrawal (Abstinence) Syndrome
Physical dependence with or without psychological dependence tends to occur on chronic administration. An abstinence syndrome may be precipitated when narcotic administration is discontinued or narcotic antagonists administered.

The following withdrawal symptoms may be observed after narcotics are discontinued: body aches, diarrhoea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, chills, tremors or shivering, stomach cramps, nausea, trouble with sleeping, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate medical use of narcotics and gradual withdrawal from the drug, these symptoms are usually mild.
4.9 OVERDOSE

Symptoms and Signs

Serious morphine overdosage is characterised by respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia, and pin point pupils (dilated if hypoxia is severe). Severe overdosage may result in apnoea, circulatory collapse, cardiac arrest and death.

Treatment

Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose of one of the antagonists should therefore be administered, preferably by the intravenous route. The usual initial intravenous (I.V.) adult dose of naloxone is 0.4 mg or higher (please refer to Naloxone Data Sheet for specific directions). Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of morphine may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonists should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

In an individual physically depended on narcotics, the administration of the usual dose of narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of narcotic antagonists in such individuals should be avoided if possible. If a narcotic antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Evacuation of gastric contents may be useful in removing unabsorbed drug.

Toxicity

Morphine toxicity may result from overdosage but because of the great inter-individual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal.

The presence of pain or tolerance tends to diminish the toxic effects of morphine. Published data suggest that in a morphine naive, pain-free individual, the lethal dose would be in excess of 120 mg. Patients on chronic oral morphine therapy have been known to take in excess of 3000 mg/day with no apparent toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS PROPERTIES

Morphine is the principal alkaloid of opium and is a phenanthrene derivative.

Morphine, like other opioids, acts as an agonist interacting with stereo-specific and saturable binding sites/receptors in the brain, spinal cord and other tissues. These sites have been classified as μ receptors and are widely distributed throughout the central nervous system being present in highest concentration in the limbic system (frontal and temporal cortex, amygdala and hippocampus), thalamus, striatum, hypothalamus, midbrain and laminae I, II, IV and V of the dorsal horn in the spinal cord. It has been postulated that exogenously administered morphine exerts its analgesic effect, in part, by altering the central release of neurotransmitter from afferent nerves sensitive to noxious stimuli.
Peripheral threshold or responsiveness to noxious stimuli is unaffected leaving monosynaptic reflexes such as the patella or the Achilles tendon reflex intact.

Morphine exerts its primary effects on the central nervous system and organs containing smooth muscle. Pharmacological effects include analgesia, drowsiness, alteration in mood (euphoria), reduction in body temperature, dose-related depression of respiration, interference with adrenocortical response to stress (at high doses), reduction in peripheral resistance with little or no effect on cardiac index, cough suppressions mediated through a direct effect on the medullary centre and miosis.

Direct stimulation of the chemoreceptor trigger zone may cause emesis and spasmogonic effects on the gastrointestinal tract resulting in decreased peristaltic activity. Urinary retention may occur due to increased bladder sphincter tone.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Morphine is readily absorbed from the gastrointestinal tract. Significant first-pass metabolism occurs in the liver following oral administration; hence, the bioavailability of oral morphine is low and variable.

With repeated regular dosing, oral morphine is about 1/3 as potent as when given by intramuscular injection.

Distribution, Metabolism and Elimination
Morphine is distributed throughout the body, but particularly to parenchymatous tissue such as kidney, lung, liver and spleen. Lower concentrations are found in skeletal muscle and brain tissue. Morphine diffuses across the placenta and trace amounts are found in sweat and breast milk. About 35% is protein bound, mainly to albumin. Morphine is metabolised principally in the liver by conjunction with glucuronic acid at the 3-hydroxyl group, and to a much lesser extent to the 3,6-diglucuronide. Elimination half-life is approximately 1.5-2 hours in healthy subjects and 90% of the dose is recovered in urine within 24 hours. Approximately 7-10% of the dose is recovered in faeces, the majority after conjugation and excretion via bile.

5.3 PRECLINICAL SAFETY DATA
There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the datasheet.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Citric acid, sodium citrate dihydrate, disodium edetate and glycerol with sodium methyl hydroxybenzoate 0.2% w/v as preservative and Water for Injections.

6.2 INCOMPATIBILITIES
Morphine is liable to precipitate out of solution in an alkaline environment.

6.3 SHELF LIFE
Store below 30°C. Discard any unused solution 6 months after opening.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Do not refrigerate. Protect from light. Discard any unused solution 6 months after opening.

6.5 NATURE AND CONTENTS OF CONTAINER
Morphine Hydrochloride 1 mg/mL, 2 mg/mL, 5 mg/mL, 10 mg/mL each available in a 200 mL bottle.
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
If only part used, discard the remaining solution.
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE
Controlled Drug B1

8. SPONSOR
Pfizer New Zealand Ltd
PO Box 3998
Shortland Street
Auckland 1140
NEW ZEALAND

Toll free number: 0800 736 363

9. DATE OF FIRST APPROVAL
27 August 1992

10. DATE OF REVISION OF THE TEXT
31 May 2017

SUMMARY TABLE OF CHANGES

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<th>Section</th>
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</thead>
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<tr>
<td>4.4</td>
<td>• Addition of the text regarding risks from concomitant use of benzodiazepines with opioids</td>
</tr>
<tr>
<td>4.5</td>
<td>• Addition of the table regarding benzodiazepines and other Central Nervous System (CNS) Depressants</td>
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