1 PRODUCT NAME  
SEVREDOL® 10 mg and 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION  
Each tablet contains morphine sulphate 10mg or 20mg.  
Excipient with known affect: Lactose, anhydrous  
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM  
SEVREDOL tablets are capsule shaped, biconvex, scored, film-coated tablets approximately 12 mm in length with the strength on one side and "IR" on the other side of the score line. The colours of the tablets are as follows: 10 mg blue and 20 mg pink.

4 CLINICAL PARTICULARS  
4.1 Therapeutic indications  
SEVREDOL tablets are indicated for the relief of both acute and chronic severe pain in adults and children aged three years and above.

4.2 Dose and method of administration  
Dose  
Adults and children over 12 years:  
SEVREDOL tablets should be given every four hours. The dosage is dependent upon the nature and severity of the pain, the patient’s condition and their previous history of analgesic therapy. A patient initially presenting with severe and intractable pain will normally be started on SEVREDOL 10 mg every 4 hours. This dose should be increased every 4 hours until the patient is free of pain. At that stage the patient should be transferred onto a long acting morphine preparation.  
To do this, add the amount of morphine needed to completely relieve pain over a 24-hour period. Divide this total in half, rounding up to nearest tablet strength and administer the long acting morphine preparation as a twice daily dose. The first dose of the long acting morphine preparation should be given with the last dose of SEVREDOL tablets. Any recurrence of pain will require an increase in the dose but not the frequency of the long acting morphine preparation. Breakthrough pain should be treated with SEVREDOL tablets, not extra long acting morphine.  
There is no upper dose limit for morphine sulphate tablets. Patients on chronic oral morphine therapy have been known to take in excess of 3000 mg/day with no apparent toxicity or addiction. The dose of morphine used for individual patients must be that dose which completely eliminates their pain irrespective of how large it is.  
Patients receiving morphine sulphate tablets in place of parenteral morphine should be given a sufficiently increased dosage to compensate for the reduction in analgesic effects associated with orally administered analgesics.
Paediatric population:
3-5 years: 5 mg 4 hourly.
6-12 years: 5-10 mg 4 hourly.

Elderly:
5 mg 4 hourly increasing as necessary to completely relieve the pain.

Method of administration:
SEVREDOL tablets should be swallowed whole and not chewed unless half tablets are being used. The tablets are film coated to mask the bitter taste of morphine and this masking effect is lost if the tablets are broken.
SEVREDOL tablets are substitutable with oral morphine solution when titrating for pain relief or treating break through pain.

4.3 Contraindications
Morphine is contraindicated in patients
• with hypersensitivity to the active substance or to any of the excipients listed in section 6.1
• with known morphine sensitivity
• with acute hepatic disease.
• with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
• with acute alcoholism,
• with head injuries,
• in which intracranial pressure is raised.
• during an attack of bronchial asthma
• with heart failure secondary to chronic lung disease.
• who are taking or have taken monoamine oxidase inhibitors (MAOIs) within the previous two weeks
• with paralytic ileus, acute abdomen, or delayed gastric emptying
• for use as a pre-operative medication.
• with pheochromocytoma, as morphine appears to increase catecholamine levels.
• with chronic pain not due to malignancy who have a prior history of substance abuse.

4.4 Special warnings and precautions for use
Respiratory depression and sedation
The major risk of opioid excess is respiratory depression.
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of SEVREDOL® 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 SEVREDOL® 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).

**Special risk patients**

Morphine should be given with caution or in reduced doses in patients with impaired kidney or liver function, biliary tract disorders, the elderly, and in patients with Addison’s disease, hypothyroidism, prostatic hypertrophy, raised intracranial pressure, hypotension with hypovolemia, pancreatitis, severe chronic obstructive lung disease, severe cor pulmonale, severe bronchial asthma or respiratory depression or urethral stricture.

Opioid analgesics such as morphine sulphate should be used with caution in patients with myasthenia gravis.

Morphine may lower the seizure threshold in patients with a history of epilepsy.

**Drug dependence and tolerance**

Narcotic analgesics may cause respiratory depression and dependence in the newborn infant. Use in pregnancy and breast-feeding is therefore not recommended.

Morphine may impair the mental and/or physical abilities needed for driving a car or operating machinery. Patients should be cautioned accordingly.

As with other narcotics, tolerance and physical dependence tend to develop upon repeated administration of morphine and there is potential for abuse of the drug and for development of strong psychological dependence. Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with morphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Morphine has an abuse profile similar to other strong agonist opioids. Morphine may be sought and abused by people with latent or manifest addiction disorders. The development of psychological dependence (addiction) to opioid analgesics, including morphine. SEVREDOL should be used with particular care in patients with a history of alcohol and drug abuse.

**Pre and post-operative use**

Morphine is not recommended preoperatively or within the first 24 hours post operatively.
**Impaired Respiration**
The respiratory depressant effects of morphine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions, including confusion, miosis and vomiting, which may obscure the clinical course of patients with head injuries.

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

**Hyperalgesia**
Hyperalgesia that will not respond to a further dose increase of morphine may very rarely occur in particular at high doses. A morphine dose reduction or change in opioid may be required.

**Hypotensive Effect**
The administration of morphine may result in severe hypotension in the post-operative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, shock, or the administration of such drugs as the phenothiazines or certain anaesthetics. Morphine may produce orthostatic hypotension in ambulatory patients.

**Supraventricular Tachycardias**
Because of possible vagolytic action that may produce a significant increase in the ventricular response rate, morphine should be used with caution in patients with atrial flutter and other supraventricular tachycardias.

**Acute Abdominal Conditions**
The administration of morphine or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Morphine should be used with caution in patients with inflammatory or obstructive bowel disorders, or with ulcerative colitis, and should only be used when necessary in patients with acute pancreatitis.

**Renal or Hepatic Disease**
Morphine may have a prolonged duration and cumulative effect in patients with kidney or liver dysfunction. In these patients, analgesia may be prolonged. Caution should be observed when morphine is administered to patients with impaired renal function, as the pharmacologically active metabolite, morphine-6-glucuronide, may accumulate in these patients. This may lead to CNS and respiratory depression.

**4.5 Interaction with other medicines and other forms of interaction**
Acidifying agents generally increase the clearance of morphine, thus antagonising its effects, while alkalising agents decrease clearance and so potentiate the effects of morphine.
**Benzodiazepines and other Central Nervous System (CNS) Depressants:**
Morphine should be used with great caution and in reduced dosage in patients concurrently receiving other central nervous system depressants including other opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, other tranquilisers, gabapentin and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Significant impairment of motor function has also been noted following concomitant morphine administration and alcohol ingestion. Concurrent administration with tricyclic antidepressants or beta-blockers may enhance the CNS depressant effects of morphine. Diazepam, when used following high doses of morphine, exacerbates the hypotensive effects produced by morphine, and is associated with reduced plasma catecholamine levels.

<table>
<thead>
<tr>
<th>Benzodiazepines and other CNS Depressants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td><strong>Examples</strong></td>
</tr>
</tbody>
</table>

**Antihypertensive Agents:**
Concurrent administration of morphine may increase the hypotensive effects of antihypertensive agents or other drugs with hypotensive effects.

**Muscle Relaxants:**
Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

**Mixed Agonist/Antagonist Opioid Analgesics:**
From a theoretical perspective, mixed agonist/antagonist opioid analgesics (e.g. pentazocine and buprenorphine) should **NOT** be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

**Monoamine Oxidase Inhibitors (MAOIs):**
MAOIs intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion, and significant depression of respiration, sometimes leading to coma. Morphine should not be given to patients taking MAOIs or within 14 days of stopping such treatment. It is unknown whether there is an interaction between the new selective MAOIs (e.g. moclobemide and selegeline) and morphine. Therefore, caution is advised with such drug combinations.

**Cimetidine and Other H2 Receptor Antagonists:**
There is a report of confusion and severe respiratory depression when a haemodialysis patient was administered morphine and cimetidine. A potentially lethal interaction between cimetidine and
morphine, in which the patient exhibited apnoea, a significantly reduced respiratory rate and suffered a grand mal seizure, has been reported. Administration of naloxone increased the respiratory rate; however, confusion, disorientation, generalised twitching and periods of apnoea persisted for 80 hours. Confusion has also been associated with concomitant use of ranitidine and morphine.

**Diuretics:**
Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

**Phenothiazines:**
The analgesic effect of morphine is potentiated by chlorpromazine.

**Amphetamines:**
Dexamphetamine and other amphetamines may enhance the analgesic effects, and decrease the sedation and lack of alertness caused by morphine.

**Anticoagulants:**
Morphine may potentiate the anticoagulant activity of coumarin anticoagulant agents.

**Metoclopramide:**
Morphine may antagonise the effects of metoclopramide on gastrointestinal motility. Intravenous metoclopramide antagonises the effects of morphine on gastric emptying.

**Zidovudine:**
Morphine may alter the metabolism of zidovudine, by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Zidovudine and morphine should therefore not be administered concurrently, because the toxicity of either or both of these drugs may be increased.

**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 activity.

**Oral Drugs:**
Morphine delays gastric emptying, so may affect the absorption of orally administered drugs. For example, morphine delays the absorption of paracetamol and mexiletine.

**Anticholinergic Agents:**
Concurrent administration of morphine and anticholinergic agents or other drugs with anticholinergic activity may increase the risk of severe constipation; this may lead to paralytic ileus and/or urinary retention.

**Antidiarrhoeal Agents:**
Concurrent administration of morphine and antidiarrhoeal agents with antiperistaltic actions may increase the risk of severe constipation and CNS depression.
**Opioid Antagonists:**
Naloxone antagonises the analgesic, CNS and respiratory depressive effects of morphine, and may precipitate withdrawal in patients who are physically dependent on opioids. Naltrexone blocks the therapeutic effects of opioids, so should be discontinued several days prior to elective surgery if administration prior to, during, or following surgery is unavoidable. Administration of naltrexone to a patient who is physically dependent on morphine will precipitate withdrawal symptoms.

**Effect on Laboratory Tests:**
Morphine delays gastric emptying, thereby invalidating test results in gastric emptying studies. Morphine may interfere with hepatobiliary imaging using technetium Tc99m diasfenin. Morphine may constrict the sphincter of Oddi and increase biliary tract pressure, preventing delivery of Tc99m diasfenin to the small bowel. These actions result in delayed visualisation, and thus resemble obstruction of the common bile duct.

### 4.6 Fertility, pregnancy and lactation

#### Pregnancy

*Category C*
Morphine has been associated with foetal CNS defects in rodent studies. It is not known whether morphine can cause foetal harm in humans when administered during pregnancy. Pregnant patients should only be given morphine when the benefits clearly outweigh potential risks to the foetus.

Long term use of morphine during pregnancy may result in a neonatal opioid withdrawal state. Babies born to mothers who are physically dependent on morphine may also be physically dependent on the drug.

#### Breastfeeding
Morphine is excreted in human milk and breast-feeding is not recommended while a patient is receiving morphine. Withdrawal symptoms have been observed in breast-fed infants when maternal administration of morphine is stopped.

#### Fertility
Prolonged use of opioid drugs may result in impairment of reproductive function, including infertility and sexual dysfunction in both sexes and irregular menses in women.

### 4.7 Effects on ability to drive and use machines
Patients should be warned that morphine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Morphine in combination with other opioid analgesics, phenothiazines, sedative-hypnotics and alcohol has additive depressant effects.

### 4.8 Undesirable effects
The adverse effects listed below are classified by body system according to their incidence (common \([\geq 1\%]\) or uncommon \([< 1\%]\)).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Common (1/100 to &lt; 1/10)</th>
<th>Uncommon (1/1,000 to &lt;1/100)</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td>Anaphylactic reaction</td>
<td>Anaphylactoid reaction</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Confusion, Insomnia</td>
<td>Agitation, Euphoria, Hallucinations, Mood altered</td>
<td>Thinking disturbances, Drug dependence, Dysphoria</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, Headache, Involuntary muscle contractions, Somnolence</td>
<td>Convulsions, Hypertonia, Paraesthesia, Syncope</td>
<td>Hyperalgesia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbance</td>
<td>Miosis</td>
<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
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<tr>
<td>Vascular disorders</td>
<td>Facial flushing, Hypotension</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pulmonary oedema, Respiratory depression, Bronchospasm</td>
<td>Cough decreased</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, Constipation</td>
<td>Abdominal pain, Anorexia, Dry mouth, Vomiting</td>
<td>Ileus, Taste perversion, Dyspepsia</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>Increased hepatic enzyme</td>
<td>Biliary pain</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Hyperhidrosis, Rash</td>
<td>Urticaria</td>
<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Urinary retention</td>
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</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Amenorrhea, Decreased libido, Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia, Fatigue, Malaise, Pruritus</td>
<td>Peripheral oedema</td>
<td>Drug tolerance, Drug withdrawal syndrome, Drug withdrawal syndrome neonatal</td>
</tr>
</tbody>
</table>

**Withdrawal (Abstinence) Syndrome:**

Chronic use of opioid analgesics may be associated with the development of physical dependence, with or without psychological dependence. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered. Withdrawal symptoms that may be observed after discontinuation of opioid use include; body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

### 4.9 Overdose

**Symptoms**

Serious morphine overdosage is characterised by respiratory depression, extreme somnolence progressing to stupor or coma, pneumonia aspiration, miotic pupils, rhabdomyolysis progressing to renal failure, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia. Severe overdosage may result in apnoea, circulatory collapse, cardiac arrest and death. The triad of coma, pinpoint pupils, & respiratory depression is considered indicative of overdosage; dilatation of the pupils occurs as hypoxia develops.

**Treatment**

A patent airway must be maintained. The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: natural opium alkaloid, ATC code: N02A A01

Morphine sulphate is the pentahydrate of the sulphate of 7,8-didehydro-4,5-epoxy-17-methyl morphinan-3,6-diol. It has a molecular formula and weight of \((C_{17}H_{19}NO_3)_2\cdot H_2SO_4\cdot 5H_2O\) and 758.8 respectively.

Morphine is a potent opioid analgesic. It is about 8 times more potent than pethidine and 10 times more potent than codeine. Morphine combines selectively at opioid binding sites found in the CNS and smooth muscle to produce its pharmacologic effects. These are due to morphine mimicking the action of endogenous endorphins, which are released in response to pain and other stimuli. Morphine relieves most types of pain but is more effective against dull, constant pain than sharp, intermittent pain. Analgesia at the supraspinal level results principally from combination with (mu) receptors, and the (kappa) receptors are responsible primarily for expression of analgesia at the spinal level. In addition to relieving severe constant pain, morphine also alleviates the associated anxiety.

**Central Nervous System**

Pharmacological effects include analgesia, drowsiness, mental clouding and mood alteration (euphoria or dysphoria). Such effects may be common at first but tolerance develops on prolonged administration. Other centrally mediated effects include respiratory depression, nausea and vomiting, to which a high degree of tolerance also develops over time.

Morphine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of haemorrhagic or ischaemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.
**Gastrointestinal Tract and Other Smooth Muscle**
Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation.

**Cardiovascular System**
Morphine may produce release of histamine with or without associated peripheral vasodilatation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

**5.2 Pharmacokinetic properties**
The onset of action of SEVREDOL tablets is about 15-30 minutes after oral administration. The duration of action is 3-4 hours.

Morphine is well absorbed from the GI tract following administration of SEVREDOL tablets, however, it is subject to extensive first-pass metabolism in the liver. SEVREDOL tablets produce peak morphine levels approximately one hour post-dose. The elimination half-life of morphine is 2-3 hours with great interpatient variability.

Like other phenanthrene derivatives, morphine is mainly metabolised by glucuronide conjugation in the liver. The resultant metabolites are excreted primarily in the urine. The principal metabolites are active, although the relative contributions of these, and parent morphine, to the overall analgesic effect is unclear. The 6-glucuronide metabolite has been shown to be 10 times more potent than parent morphine, however, the 3-glucuronide metabolite may antagonise this effect.

Morphine is widely distributed through the body and diffuses across the placenta. Reduced dosing is necessary in patients with renal or hepatic dysfunction, and also in the elderly due to increased sensitivity to its effect.

**5.3 Preclinical safety data**
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Data Sheet.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

**Core:**
- Lactose anhydrous
- Pregelatinised maize starch
- Povidone K25
- Magnesium stearate
- Purified talc.

**10 mg tablet:**

**Coat:**
- Hydroxypropylmethyl cellulose
- Polyethylene glycol 400
- Opadry 06B20843.
20 mg tablet:

Coat:
Hydroxypropylmethyl cellulose
Polyethylene glycol 400
Opaspray M-1-5503.

6.2 Incompatibilities
None known

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 30 °C. Protect from light and moisture. Keep out of reach of children.

6.5 Nature and contents of container
10 mg or 20 mg tablets, packed in bottles or blister packs of 10

6.6 Special precautions for disposal
No special requirements

7 MEDICINE SCHEDULE
Controlled Drug B1.

8 SPONSOR
Distributed on behalf of Mundipharma New Zealand Limited by:
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P O Box 4079
AUCKLAND 1140
Ph: (09) 377-3336
Toll Free [Medical Enquiries]: 0800 773 310

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10 DATE OF REVISION OF THE TEXT
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(CCDS dated 07 April 2017 V14)
Orbis NZR-0052
### SUMMARY TABLE OF CHANGES

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<td>Reformatted to new SPC format</td>
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<tr>
<td>Section 4.4</td>
<td>Additional information about risks of concomitant use with benzodiazepines and other CNS depressants as per MARC review</td>
</tr>
<tr>
<td>Section 4.5</td>
<td>Addition of interaction with benzodiazepines and other CNS depressants as per MARC review</td>
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<tr>
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