SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Naloxone Hydrochloride Injection 1mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Naloxone Hydrochloride 1 mg/ml

3. PHARMACEUTICAL FORM

An isotonic, sterile Solution for Injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Naloxone may be used for the complete or partial reversal of opioid depression, including mild to severe respiratory depression induced by natural and synthetic opioids, including dextropropoxyphene, methadone and certain mixed agonist/antagonist analgesics: nalbuphine and pentazocine. It may also be used for the diagnosis of suspected acute opioid overdosage. Naloxone may also be used to counteract respiratory and other CNS depression in the newborn resulting from the administration of analgesics to the mother during childbirth.

4.2. Posology and method of administration

Naloxone is for intravenous, intramuscular or subcutaneous injection or intravenous infusion.

Intravenous infusion: Naloxone may be diluted for intravenous infusion in normal saline (0.9%) or 5% dextrose in water or saline; the addition of 2mg
(2ml of 1mg/1ml concentration) of Naloxone in 500ml of either solution provides a concentration of 4 micrograms/ml. Mixtures should be used within 12 hours. After 12 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient’s response to both Naloxone infusion and to any previous bolus doses administered.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

**Adults:**

**Opioid overdosage (known or suspected)**

An initial dose of 400 to 2000 micrograms of Naloxone may be administered intravenously. If the desired degree of counteraction and improvement in respiratory function is not obtained it may be repeated at 2 to 3 minute intervals. If no response is observed after 10mg of Naloxone have been administered the diagnosis of opioid-induced or partial opioid induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if dosing by the intravenous route is not feasible.

N.B. The duration of action of certain opioids can outlast that of an IV bolus of Naloxone, e.g. dextropropoxyphene (present in commonly prescribed analgesics which in over-dosage have been associated with suicide), dihydrocodeine and methadone. In situations where one of these opioids is known or suspected it is recommended that an infusion of Naloxone be used to produce sustained antagonism to the opioid without repeated injection.

**Post Operative Use**

When Naloxone is used postoperatively, the dose should be titrated for each patient in order to obtain optimum respiratory response while maintaining adequate analgesia. Intravenous doses of 100-200 micrograms (approximately 1.5-3 micrograms/kg body weight) are usually sufficient, but a full two minutes should be allowed between each 100 micrograms increment of Naloxone administered. Further intramuscular doses may be needed within one to two hours, depending on the interval since the last opioid administration and the amount and type (i.e. long or short-acting) of drug used. Alternatively Naloxone may be administered as an intravenous infusion (see above).

**Children**

The usual initial dose in children is 10 micrograms/kg body weight given i.v. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 100 micrograms/kg of bodyweight may be administered. Naloxone may be required by infusion as described above. If an i.v. route of administration is not feasible, Naloxone may be administered i.m. or s.c. in divided doses.
Neonatal Use

An adequate airway should be established in the apnoeic infant before Naloxone is administered. The usual dose is for opioid-induced depression is 10 micrograms/kg body weight administered i.v., i.m., or s.c.. If the desired degree of counteraction and improvement in respiratory function is not obtained it may be repeated at 2-3 minute intervals. Alternatively, a single dose of 200 micrograms, approximately 60 micrograms/kg body weight may be given intramuscularly at birth.

It should, however, be noted that onset of action is slower following i.m. injection. In neonates needing infusion of Naloxone in saline, care should be taken to avoid excessive sodium intake.

Elderly

There have been no specific studies for use in the elderly.

4.3. Contraindications

Naloxone should not be given to patients who are known to be hypersensitive to the drug.

4.4. Special warnings and precautions for use

It should be administered cautiously to patients who have received large doses of opioids or to those physically dependent on opioids since too rapid reversal of opioid effects by Naloxone may precipitate an acute withdrawal syndrome in such patients. The same caution is needed when giving Naloxone to neonates delivered of such patients.

The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include but are not limited to the following: body aches, diarrhoea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea, vomiting, nervousness, restlessness, irritability, shivering, trembling, abdominal cramps, weakness and increased blood pressure. In the neonate, opioid withdrawal may also include: convulsions, excessive crying and hyperactive reflexes.

Patients who have responded satisfactorily to Naloxone should be kept under observation. Repeated doses of Naloxone may be necessary since the duration of action of some opioids may exceed that of Naloxone.

Naloxone is not effective against respiratory depression caused by non-opioid drugs. Reversal of buprenorphine-induced respiratory depression may be
incomplete. If an incomplete response occurs, respiration should be mechanically assisted.

Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary oedema and cardiac arrest which may result in death.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary oedema and cardiac arrest have been reported in postoperative patients. Death, coma and encephalopathy have been reported as sequelae of these events. Although a direct cause and effect relationship has not been established, Naloxone should be used with caution in patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation and pulmonary oedema.

In addition to Naloxone, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage and vasopressor agents should be available and employed when necessary to counteract acute poisoning.

Renal Insufficiency/Failure: The safety and effectiveness of Naloxone in patients with renal insufficiency/failure have not been established in clinical trials. Caution should be exercised and patients monitored when Naloxone is administered to this patient population.

Liver disease: The safety and effectiveness of Naloxone in patients with liver disease have not been established in well-controlled clinical trials. In one small study in patients with liver cirrhosis, plasma naloxone concentrations were approximately six times higher than in patients without liver disease. Naloxone administration had a diuretic effect in these patients with cirrhosis. Caution should be exercised when Naloxone is administered to a patient with liver disease.

4.5. **Interaction with other medicinal products and other forms of interaction**

Naloxone should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

4.6. **Pregnancy and lactation**

Pregnancy
The safety of this medicinal product for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri- and postnatal development. Naloxone should, like all drugs, be used with caution during pregnancy.

In a pregnant woman who is known or suspected to be opioid-dependent, risk benefit must be considered before Naloxone is administered, since maternal dependence may be accompanied by foetal dependence. In this type of circumstance, the neonate should be monitored for respiratory rate and signs of opioid withdrawal.

Use in Labour and Delivery

Naloxone may be administered to mothers during the second stage of labour to correct respiratory depression caused by opioids used to provide obstetrical analgesia.

It is not known if Naloxone affects the duration of labour and/or delivery.

Lactation

It is not known whether Naloxone is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when Naloxone is administered to a nursing mother.

4.7. Effects on ability to drive and use machines

Not Applicable

4.8. Undesirable effects

Postoperative: The following adverse effects have been associated with the use of Naloxone in postoperative patients: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnoea, pulmonary oedema, and cardiac arrest. Death, coma and encephalopathy have been reported as sequelae of these events. Excessive doses of Naloxone in postoperative patients may result in significant reversal of analgesia and may cause agitation.

Opioid Depression: Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary oedema and cardiac arrest which may result in death (see Special Warnings).

Opioid Dependence: Abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate an acute withdrawal
syndrome which may include, but is not limited to the following signs and symptoms: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering, trembling, nervousness, restlessness, irritability, diarrhoea, nausea, vomiting, abdominal cramps, increased blood pressure and tachycardia. In the neonate, opioid withdrawal may also include convulsions, excessive crying and hyperactive reflexes (see Special Warnings).

Agitation and paraesthesias have been infrequently reported with the use of Naloxone.

4.9 Overdose

There is limited clinical experience with Naloxone overdosage in humans.

**Adult Patients:** In one study, volunteers and morphine-dependent subjects who received a single subcutaneous dose of 24mg/70kg did not demonstrate toxicity.

In another study, 36 patients with acute stroke received a loading dose of 4mg/kg (10mg/m²/min) of Naloxone followed immediately by 2mg/kg/hr for 24 hours. There were a few reports of serious adverse events: seizures (2 patients), severe hypertension (1) and hypotension and/or bradycardia (3).

At doses of 2 mg/kg in normal subjects, memory impairment has been reported.

**Paediatric Patients:** Up to 11 doses of 0.2mg of naloxone (2.2mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulphate. Paediatric reports include a 2½ year old child who inadvertently received a dose of 20mg of naloxone and a 4½ year old child who received 11 doses during a 12-hour period, both of whom had no adverse sequelae.

**Patient Management:** Patients who experience a Naloxone overdose should be treated symptomatically in a closely-supervised environment. Physicians should contact a poison control centre for the most up-to-date patient management information.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Naloxone is a competitive antagonist of µ, δ and κ-opioid receptors. Naloxone is most potent at the µ-receptor. Naloxone, given on its own, produces very little effect. However, if it is given in higher doses it rapidly reverses the effect of morphine and other opioids, including pentazocine and nalorphine. Naloxone has little effect on the pain threshold in normal conditions, but causes hyperalgesia in stressful conditions where endogenous opioids are produced. Naloxone also inhibits acupuncture analgesia, which is associated with the release of opioid peptides. Naloxone also prevents analgesia produced by PAG (periaqueductal grey matter) stimulation. PAG is one site of action in pain transmission. Naloxone is given intravenously and its effects are produced immediately. It is rapidly metabolised by the liver, and its effect lasts only 1-2 hours, which is a lot shorter than that of most morphine-like drugs. Thus it may have to be given repeatedly.

5.2. Pharmacokinetic properties

Naloxone is rapidly absorbed following oral administration but high presystemic metabolism makes this route unreliable. Naloxone is highly lipid soluble and is thus rapidly distributed throughout the body, with a volume of distribution of 5.1kg⁻¹. High concentrations occur in brain, kidney, lung, heart and skeletal muscle. The brain/serum ratio has been estimated to be 1.5-4.6, approximately 15 times that of morphine. Levels of naloxone in the central nervous system are short-lived as rapid redistribution occurs and this could account for the short duration of action. About 50% of naloxone is bound to plasma proteins, principally albumin. The plasma half-life is 1-2 hours. When naloxone reaches the liver it undergoes extensive biotransformation, almost none of the drug excreted being unchanged. Metabolites are excreted largely in the urine, 70% of the dose being recoverable over 72 hours. In the neonate the elimination half-life is prolonged because of reduced hepatic metabolism.

5.3. Preclinical safety data

There is no pre-clinical data of relevance to the prescriber which is additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium Chloride
Dilute Hydrochloric Acid
6.2. Incompatibilities

It is recommended that infusions of Naloxone Hydrochloride should not be mixed with preparations containing bisulphite, metabisulphite, long-chain or high molecular weight anions, or solutions with an alkaline pH (Martindale, 1996).

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5. Nature and contents of container

Sterile solution for injection presented in a Glass (Type I) 2ml prefilled syringe.

6.6. Instruction for use, handling and disposal

Use once and discard any remaining solution.

7 MARKETING AUTHORISATION HOLDER

Aurum Pharmaceuticals Ltd
Bampton Road
Harold Hill
Romford
8. MARKETING AUTHORISATION NUMBER

PL 12064/0060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/11/2005

10. DATE OF REVISION OF THE TEXT

11/11/2005