Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Narcan Neonatal 20 micrograms/ml, Solution for Injection or Infusion 2 ml Ampoule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 20 micrograms naloxone hydrochloride. Each 2 ml-ampoule of solution contains 40 micrograms naloxone hydrochloride.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear, colourless to faintly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Narcan Neonatal is indicated for the complete or partial reversal of opioid-induced depression and other CNS depression in the new-born resulting from the administration of analgesics to the mother during childbirth.

4.2 Posology and method of adminstration

Narcan Neonatal is for intravenous, intramuscular or subcutaneous injection or intravenous infusion.

Intravenous infusion: Narcan 0.4mg/ml, may be diluted for intravenous infusion in normal saline (0.9%) or 5% dextrose in water or saline: the addition of 2 mg of Narcan in 500 ml 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 the Narcan infusion and to any previous bolus doses administered.

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

An adequate airway should be established in the apnoeic infant before naloxone hydrochloride is administered. The usual dose 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 to 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 hydrochloride in saline care should be taken to avoid excessive sodium intake.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Narcan should be administered with great caution to new-borns of mothers who have received large doses of opioids or to those physically dependent on opioids since too rapid reversal of opioid effects by naloxone hydrochloride may precipitate an acute withdrawal syndrome.

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.

New-borns who have responded satisfactorily to naloxone hydrochloride should be kept under observation. Repeated doses of naloxone hydrochloride may be necessary since the duration of action of some opioids may exceed that of naloxone hydrochloride.

Naloxone hydrochloride 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. These have occurred in adult patients, most of whom had pre-existing cardiovascular disorders or received other drugs which have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, naloxone hydrochloride 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.

It has been suggested that the pathogenesis of pulmonary oedema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary oedema i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressure.

In addition to naloxone hydrochloride, 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 with opioids.

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

Liver disease: The safety and effectiveness of naloxone hydrochloride 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 hydrochloride was well tolerated and no adverse events were reported. Caution should be exercised when naloxone hydrochloride is administered to patient with liver disease.

4.5 Interaction with other medicinal products and other forms of interaction

Naloxone hydrochloride should be administered cautiously to new-borns 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

Not relevant.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Postoperative: The following adverse events have been associated with the use of naloxone hydrochloride 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 hydrochloride in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **SPECIAL WARNINGS).**

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, 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 hydrochloride.

4.9 Overdose

There is limited clinical experience with naloxone hydrochloride overdosage in humans.

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

In another study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m^2/min) of naloxone hydrochloride followed immediately by 2 mg/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 0.2 mg of naloxone (2.2 mg) 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 20 mg 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 hydrochloride 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 N-ally-nor-oxymorphone, an opioid antagonist which is devoid of the agonist or morphine-like properties characteristic of other opioid antagonists. In the absence of opioids or agonistic effects of opioid mixed agonist/antagonist it exhibits essentially no pharmacological activity.

5.2 Pharmacokinetic properties

Naloxone hydrochloride usually acts within two minutes of intravenous administration and the onset of action is only slightly less rapid following intramuscular or subcutaneous injection. The duration of action is dependent upon the dose and route of administration, with intramuscular injection producing a more prolonged effect than intravenous doses. However, the need for repeat doses of naloxone hydrochloride also depends on the amount, type and route of administration of the opioid being antagonised.

The rate of administration should be titrated in accordance with the patient's response to both the naloxone hydrochloride infusion and to any previous bolus dose.

Following parenteral administration, naloxone hydrochloride is rapidly distributed in the body. It is metabolised in the liver, primarily by glucuronide conjugation and excreted in urine. In adults the mean calculated serum half-life was 64 ± 12 minutes. In neonates the mean plasma half-life was 3.1 ± 0.5 hours following injection into the umbilical vein. In premature infants the mean calculated serum half-life was 51.8 ± 9.2 minutes.

5.3 Preclinical safety data

Naloxone hydrochloride is well established in medical use. Preclinical data is broadly consistent with clinical experience. Studies in animals to assess the carcinogenic potential of Narcan have not been conducted. Narcan was weakly positive in the Ames mutagenicity and *in vitro* human lymphocyte chromosome aberration tests and was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in an *in vivo* rat bone marrow chromosome aberration study. Reproduction studies conducted in mice and rats at doses as high as 50 times the usual human dose (10 mg/day) demonstrated no impairment of fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid
Water for injections

6.2 Incompatibilities

Narcan should not be mixed with preparations containing bisulphite, metabisulphite, long-chain or high molecular weight anions or any solution having an alkaline pH: no drug or chemical agent should be added to Narcan unless its effect on the chemical and physical stability of the solution has first been established.

6.3 Shelf Life

2 years.

Chemical and physical in-use stability has been demonstrated for 12 hours at 2-8° C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage

times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep container in the outer carton.

6.5 Nature and contents of container

Clear, Type I glass ampoules each containing 2 ml (equivalent to 40 micrograms naloxone hydrochloride) are supplied in boxes of ten ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

See section 4.2.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals Limited
Swords
County Dublin

8 MARKETING AUTHORISATION NUMBER

PA 2/71/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 June 1992

Date of last renewal: 9 June 2002

10 DATE OF REVISION OF THE TEXT

February 2003