Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Narcan 400 micrograms/ml Solution for Injection or Infusion 1 ml-ampoule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 400 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 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. Narcan Neonatal may 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 adminstration

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

Intravenous infusion: Narcan may be diluted for intravenous infusion in normal saline (0.9%) or 5% dextrose in water or saline: the addition of 2 mg (5 ml of 400 micrograms/ml concentration) 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.

ADULTS

Opioid overdosage (known or suspected)

An initial dose of 400 - 2000 micrograms of Narcan 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 10 mg of Narcan 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.

NB: The duration of action of certain opioids can outlast that of an i.v. bolus of Narcan, 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 Narcan (see above) be used to produce sustained antagonism to the opioid without repeated injection.

Post Operative Use

When Narcan is used post-operatively, 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 microgram increment of Narcan 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 Narcan 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 body weight may be administered. Narcan may be required by infusion as described above. If an i.v. route of administration is not feasible, Narcan may be administered i.m. or s.c. in divided doses.

NEONATAL USE

An adequate airway should be established in the apnoeic infant before Narcan 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 Narcan in saline care should be taken to avoid excessive sodium intake.

ELDERLY

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

4.3 Contraindications

Narcan 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 patients who have received large doses of opioids or to those physically dependent on opioids since too rapid reversal of opioid effects by Narcan may precipitate an acute withdrawal syndrome in such patients. The same caution is needed when giving Narcan 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 Narcan should be kept under observation. Repeated doses of Narcan may be necessary since the duration of action of some opioids may exceed that of Narcan.

Narcan 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 patients, most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects.

Although a direct cause and effect relationship has not been established, Narcan 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 Narcan 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 Narcan, 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 Narcan in patients with renal insufficiency/failure have not been established in well-controlled clinical trials. Caution should be exercised when Narcan is administered to this patient population.

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

4.5 Interaction with other medicinal products and other forms of interaction

Narcan should be administered with great caution 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. Narcan 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 Narcan is administered, since maternal dependence may often be accompanied by foetal dependence.

Use in Labour and Delivery

Narcan 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 Narcan affects the duration of labour and/or delivery.

Lactation

It is not known whether Narcan is excreted in human milk, therefore breast feeding is not recommended.

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 Narcan 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 Narcan in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **SPECIAL WARNINGS** and **POSOLOGY AND METHOD OF ADMINISTRATION: Usage in Adults: Postoperative Use).**

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 Narcan.

4.9 Overdose

There is limited clinical experience with Narcan 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 Narcan 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 Narcan 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-allyl-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 agonists/antagonists it exhibits essentially no pharmacologic activity.

5.2 Pharmacokinetic properties

Narcan 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 Narcan 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 Narcan infusion and to any previous bolus dose.

Following parenteral administration, Narcan 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

Narcan 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

3 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 1 ml (equivalent to 400 micrograms naloxone hydrochloride) are supplied in boxes of three and 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 2/71/3

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