IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0073/111/001
Case No: 2071149

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Antigen Pharmaceuticals Ltd

Chandler House, **Castle Street**, **Roscrea**, **Co Tipperary**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Naloxone Hydrochloride 20 micrograms/ml Solution for Injection or Infusion

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/04/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naloxone Hydrochloride 20 micrograms/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 20 micrograms (0.02mg) Naloxone Hydrochloride present as Naloxone hydrochloride dihydrate.
Each 2 ml of solution contains 40 micrograms (0.04mg) Naloxone Hydrochloride present as Naloxone hydrochloride dihydrate

Excipients: Each 1ml contains 3.53 mg sodium
Each 2 ml contains 7.06 mg sodium

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear colourless sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the reversal of opioid depression, including respiratory depression, caused by natural or synthetic opioids, the agonist-antagonists nalbuphine and pentazocine, or dextropropoxyphene. Naloxone may also be used for the diagnosis of suspected opioid overdosage. Naloxone may be used to reverse respiratory and other CNS depression in the neonate, resulting from administration of narcotic analgesics to the mother during labour.

4.2 Posology and method of administration

Naloxone is for intravenous, intramuscular or subcutaneous injection. It may also be administered by intravenous infusion.

Opioid overdosage (known or suspected):

Adults: An initial dose of 400 to 2000 micrograms (0.4mg to 2mg) of naloxone may be given intravenously and may, if required, be repeated at 2 to 3 minute intervals. The diagnosis of opioid-related toxicity should be reconsidered if there is still failure to respond after a total of 10mg of naloxone has been administered. If intravenous administration is impracticable, naloxone may be administered by the intramuscular or subcutaneous route.

The duration of action of some opioids (including dextropropoxyphene, dihydrocodeine and methadone) may exceed that of naloxone. In these circumstances, an intravenous infusion of naloxone will provide sustained antagonism of the opioid and obviate the need for repeated injections. Naloxone may be diluted for intravenous infusion in 0.9% (normal) saline or 5% dextrose in water or saline. Addition of 2mg of naloxone to 500ml of one of these solutions provides a concentration of 4 micrograms/ml (0.004mg/ml). Mixtures should be used within 24 hours and any unused solution should be discarded after this time. The rate of infusion should be titrated according to the patients response.

Post-operative use: Dosage is individually titrated to maintain adequate analgesia while gaining optimum respiratory

response. The usual intravenous dose is 100 to 200 micrograms (0.1 to 0.2mg) i.e. approximately 1.5 to 3 micrograms (0.0015 to 0.003mg) per kg bodyweight with a two minute interval between each 100 microgram (0.1mg) increment administered.
Depending on the type of opioid, the dose and the time interval from its last administration, repeat doses of naloxone may be required within one to two hours and may be administered by intramuscular injection or by intravenous infusion in order to produce a more sustained effect.

Children: The usual initial dose is 10 micrograms (0.01mg) per kg body weight, intravenously. If adequate response does not occur a dose of 100 micrograms (0.1mg) per kg body weight may be administered.
Alternatively, naloxone may be administered by intravenous infusion, if appropriate or if the I.V. route is not feasible, it may be given I.M. or S.C. in divided doses.

Neonatal Use: For opioid-induced depression, the usual initial dose is 10 micrograms (0.01mg) per kg body weight, I.V., I.M. or S.C.
This dose may be repeated, if required, at 2 to 3 minute intervals. Alternatively, a single dose of 200 micrograms (0.2mg) i.e. approximately 60 micrograms (0.06mg) per kg bodyweight may be administered intramuscularly at birth although the onset of action is slower after I.M. injection.
An adequate airway should be established prior to administering naloxone to the apnoeic infant.

4.3 Contraindications

Naloxone should not be administered to patients with a known hypersensitivity to it.

4.4 Special warnings and precautions for use

Naloxone is not effective in depression due to non-narcotic substances such as barbiturates, tranquillizers, anaesthetics etc.
Repeated dosage may be necessary in view of the prolonged duration of action of some narcotics.

Patients should be kept under constant surveillance.

Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures and cardiac arrest. In postoperative patients, larger than necessary dosage of naloxone may result in significant reversal of analgesia and excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary oedema have been associated with the use of naloxone postoperatively. (see 4.8 Undesirable effects)

Administration should be carried out only with great caution in patients who have received large doses of narcotics or are narcotic addicts, in order to avoid precipitation of an acute abstinence syndrome. Similar caution is required with neonates whose mothers have received large doses of opioids or are dependent on them.

Resuscitative measures for maintenance of a free airway, artificial ventilation, cardiac activity and blood pressure should be available.

Naloxone should be used with caution in patients with cardiac irritability.

4.5 Interaction with other medicinal products and other forms of interaction

See section 4.4

4.6 Pregnancy and lactation

Although reproduction studies in animals have not demonstrated any teratogenic or embryotoxic effects, naloxone should be administered during pregnancy only if considered essential by the physician. Naloxone crosses the placenta. It is not known whether naloxone is excreted in breast milk, therefore caution is required when naloxone is

administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Nausea and vomiting have been reported in some post-operative patients who received naloxone in doses higher than those recommended; a direct relationship has not been established.

There have been reports of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary oedema. These have occurred in postoperative 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, naloxone should be used with caution in patients with pre-existing cardiac disease or patients who have received potentially cardiotoxic drugs.

4.9 Overdose

There have been no reports of acute overdosage with naloxone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Naloxone is a specific opioid antagonist. It is an essentially pure antagonist in the sense that it does not possess agonist or morphine-like properties. Although the mechanism of the drug's action has not been fully elucidated, naloxone appears to antagonize the effects of opioids by competing for the same receptor sites. When naloxone is given intravenously, the onset of action is generally apparent within two minutes; onset of action is only slightly less rapid when the drug is administered subcutaneously or intramuscularly. The duration of action is dependent on the dose and route of administration and may be one to four hours or shorter.

5.2 Pharmacokinetic properties

Although absorbed readily from the gastrointestinal tract, naloxone undergoes extensive first-pass metabolism in the liver before reaching the systemic circulation and thus must be administered parenterally. It is rapidly absorbed from parenteral sites of injection and is metabolised in the liver, mainly by glucuronide conjugation, and excreted in urine. Naloxone has a short plasma half-life of approximately one hour after parenteral administration

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Dilute Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Naloxone should not be mixed with preparations containing bisulphite, metabisulphite, long chain or high molecular weight anions or any solution having an alkaline pH.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf Life

As packaged for sale: 4 years
Diluted solutions should be used within 24 hours and any unused solution should be discarded after this time.

6.4 Special precautions for storage

Do not store above 25°C. Keep the ampoules in the outer carton in order to protect from light.
For storage after opening and dilution, see section 6.3.

6.5 Nature and contents of container

Clear glass with green one point cut (OPC) ampoules, glass type 1 Ph. Eur. with yellow and green rings.
Pack sizes: 3x2 ml; 5x2 ml; and 10x2 ml ampoules.

Not all pack sizes may be marketed.

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

For single use only.
Naloxone may be diluted for intravenous infusion in 0.9% (normal) saline or 5% dextrose in water or saline. Addition of 2mg of naloxone to 500ml of one of these solutions provides a concentration of 4 micrograms/ml (0.004mg/ml).
Diluted solutions should be used within 24 hours and any unused solution should be discarded after this time.

7 MARKETING AUTHORISATION HOLDER

Antigen Pharmaceuticals Ltd
Chandler House
Castle Street
Roscrea
Co Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 73/111/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation : 3rd October 1989
Date of last renewal : 3rd October 2009

10 DATE OF REVISION OF THE TEXT

April 2010