Naloxone Hydrochloride 400 micrograms/ml solution for injection

PL 19364/0031

UKPAR

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Naloxone Hydrochloride 400 micrograms/ml solution for injection (Product Licence number: PL 19364/0031) on 18 February 2011.

Naloxone hydrochloride belongs to a group of medicines known as opioid antagonists. It is used to treat very shallow breathing that may be caused by opioid pain killers. It may also be used to diagnose opioid overdose.

Naloxone Hydrochloride 400 micrograms/ml solution for injection raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
NALOXONE HYDROCHLORIDE 400 MICROGRAMS/ML SOLUTION FOR INJECTION

PL 19364/0031

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted a Marketing Authorisation for the medicinal product Naloxone Hydrochloride 400 micrograms/ml solution for injection (PL 19364/0031) to UKR Regulatory Affairs Ltd. on 18 February 2011. This medicine is only available on prescription.

Naloxone is indicated for the treatment of respiratory depression induced by natural and synthetic opioids, such as codeine, diamorphine, levorphanol, methadone, morphine, concentrated opium alkaloid hydrochlorides and propoxyphene. It is also useful for the treatment of respiratory depression caused by opioid agonist/antagonists, such as nalbuphine and pentazocine. Naloxone is also used for the diagnosis of suspected acute opioid overdose.

This application is submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that Naloxone Hydrochloride 400 micrograms/ml solution for injection is a generic version of Naloxone Hydrochloride Minijet 400 micrograms/ml, solution for injection, currently licensed to International Medication Systems (UK) Ltd (PL 03265/0071). This reference product has been authorised in the EEA for over 10 years (since 29 September 1986), the legal basis of this application is, therefore, acceptable and the ten year rule is complied with.

Assurance has been provided that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

No new preclinical studies were conducted, which is acceptable given that the application is for a generic version of an originator product that has been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the application is for a generic version of an originator product that has been licensed for over 10 years.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: NALOXONE HYDROCHLORIDE

INN:        Naloxone hydrochloride
Chemical name:  4,5α-epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride 17-(Cyclobutylmethyl)-4,5α-epoxymorphinan-3,6,14-triol hydrochloride N-cyclobutylmethyl-14-hydroxydihydromorphine hydrochloride

Structure:

![Structure of Naloxone Hydrochloride](image)

Molecular formula:  C_{19}H_{22}ClNO_{4},2H_2O
Relative molecular mass:  399.9

General properties: A white or almost white, crystalline powder. Hygroscopic. Freely soluble in water, soluble in alcohol, and practically insoluble in toluene, with a melting point between 200 to 205°C and an aqueous solution pH of 2.5 to 3.5.

The naloxone hydrochloride used in this product complies with the current EDQM Certificate of Suitability and is, therefore, satisfactory.

Stability

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT: NALOXONE HYDROCHLORIDE 400 MICROGRAMS/ML SOLUTION FOR INJECTION

Description and composition

Naloxone Hydrochloride 400 micrograms/ml solution for injection is a clear, colourless solution containing naloxone hydrochloride and the pharmaceutical excipients sodium chloride, sodium hydroxide, hydrochloric acid and water for injection. All excipients comply with the specifications in their respective European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all excipients.

Pharmaceutical development

The objective of the pharmaceutical development programme was to formulate a robust, stable, solution for injection equivalent to the reference product, Naloxone Hydrochloride Minijet 400 micrograms/ml, solution for injection and exhibiting the same bioavailability in order to comply with the regulations pertaining to generic medicinal product applications.
Suitable pharmaceutical development data have been provided for this application. The physico-chemical properties of the drug product have been compared with those of the originator product. These data demonstrate that the proposed product can be considered a generic version of Naloxone Hydrochloride Minijet 400 micrograms/ml, solution for injection.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

**Finished product specification**
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

**Container closure system**
The product is contained in a glass ampoule (Type I) of 1ml. The product is available in boxes of 10 ampoules.

Specifications and certificates of analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been set for the product when it is stored in the original packaging.

**Expert report**
A satisfactory expert report is provided from an appropriately qualified author.

**Product literature**
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Pharmaceutical conclusion**
It is recommended that a Marketing Authorisation is granted for this application.
**PRECLINICAL ASSESSMENT**

As the pharmacodynamic, pharmacokinetic and toxicological properties of naloxone hydrochloride are well-known, no further preclinical studies are required and none have been provided.

The applicant’s preclinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a preclinical viewpoint.
CLINICAL ASSESSMENT

Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), point 5.1.6, a bioequivalence study is not requested if the product is an aqueous intravenous solution containing the same active substance in the same concentration as the currently licensed reference product.

Efficacy
No new data on the efficacy of this product have been submitted and none are required for this type of application.

Safety
No new or unexpected safety issues were raised for this application.

Product literature
The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

Pharmacovigilance system
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk management plan (RMP)
The applicant has not submitted an RMP, nor is one needed for an application of this kind.

Clinical expert report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Naloxone Hydrochloride 400 micrograms/ml solution for injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of naloxone hydrochloride is well established.

SAFETY
No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with naloxone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk: benefit ratio is, therefore, considered to be acceptable for this product and a Marketing Authorisation may be granted.
**STEPS TAKEN FOR ASSESSMENT**

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1 NAME OF THE MEDICINAL PRODUCT
Naloxone Hydrochloride 400 micrograms/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ampoule of 1 ml contains 440 micrograms Naloxone hydrochloride as dihydrate, equivalent to 400 micrograms Naloxone hydrochloride.

Each 1 ml ampoule also contains 3.5 mg (0.154 mmol) of sodium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.
Clear colourless solution.
pH 3.0 to 4.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Naloxone is indicated for the treatment of respiratory depression induced by natural and synthetic opioids, such as codeine, diamorphine, levorphanol, methadone, morphine, concentrated opium alkaloid hydrochlorides and propoxyphene. It is also useful for the treatment of respiratory depression caused by opioid agonist/antagonists nalbuphine and pentazocine. Naloxone is also used for the diagnosis of suspected acute opioid overdose.

4.2 Posology and method of administration
Naloxone hydrochloride may be administered by IV, IM or SC injection or IV infusion.

Adults:
For instructions on preparation see section 6.6.

Naloxone hydrochloride may be used postoperatively to reverse central depression resulting from the use of opioids during surgery. The usual dosage is 100 - 200 micrograms IV given at 2 to 3 minute intervals to obtain optimum respiratory response while maintaining adequate analgesia. Additional doses may be necessary at one to two hour intervals depending on the response of the patient and the dosage and duration of action of the opioid administered.

For the treatment of known opioid overdosage or as an aid in the diagnosis of suspected opioid overdosage, the usual initial adult dosage of naloxone hydrochloride is 400 - 2000 micrograms IV, administered at 2 to 3 minute intervals if necessary. If no response is observed after a total of 10 mg of the
drug has been administered, the depressive condition may be caused by a drug or disease process not responsive to naloxone. When the IV route cannot be used, the drug may be administered by IM or SC injection.

Children:

The usual initial dose in children is 10 micrograms / kg bodyweight given IV. If the dose does not result in the desired degree of clinical improvement, a subsequent dose of 100 micrograms / kg body weight may be administered. If the IV route of administration is not available, naloxone may be administered IM or SC in divided doses. If necessary, naloxone can be diluted with sterile water for injection.

Opoid-induced depression in neonates resulting from the administration of opioid analgesics to the mother during labour may be reversed by administering naloxone hydrochloride 10 micrograms / kg body weight to the infant by IM, IV or SC injections, repeated at intervals of 2 to 3 minutes if necessary. Alternatively, a single IM dose of about 60 micrograms / kg may be given at birth for a more prolonged action.

Elderly:

In elderly patients with pre-existing cardiovascular disease or in those receiving potentially cardiotoxic drugs, naloxone should be used with caution since serious adverse cardiovascular effects such as ventricular tachycardia and fibrillation have occurred in postoperative patients following administration of naloxone.

4.3 Contraindications
Naloxone is contraindicated in patients with known hypersensitivity to the drug, or to any of the excipients. (For excipients, see section 6.1)

4.4 Special warnings and precautions for use
It should be administered with caution to patients who have received large doses of opioids or to those physically dependent on opioids since too rapid reversal may precipitate an acute withdrawal syndrome in such patients. When naloxone hydrochloride is used in the management of acute opioid overdose, other resuscitation measures should be readily available. A withdrawal syndrome may also be precipitated in newborn infants of opioid-dependent mothers.

Following the use of opioids during surgery, excessive dosage of naloxone hydrochloride should be avoided, because it may cause excitement, increase in blood pressure and clinically important reversal of analgesia. A reversal of opioid effects achieved too rapidly may induce nausea, vomiting, sweating or tachycardia.

Naloxone should be also used with caution in patients with pre-existing cardiovascular disease or in those receiving potentially cardiotoxic drugs, since serious adverse cardiovascular effects such as ventricular tachycardia
and fibrillation have occurred in postoperative patients following administration of naloxone.

Patients who have responded to naloxone should be carefully monitored, since the duration of action of some opioids may exceed that of naloxone.

4.5 Interaction with other medicinal products and other forms of interaction

No drug or chemical agent should be added to naloxone unless its effect on the chemical and physical stability of the solution has first been established.

4.6 Pregnancy and lactation

Reproductive studies in mice and rats using naloxone hydrochloride dosage up to 1000 times the usual human dosage have not revealed evidence of impaired fertility or harm to the foetus. There are no adequate and controlled studies using the drug in pregnant women. Naloxone hydrochloride should be used only when clearly needed. Since it is not known whether naloxone hydrochloride is distributed into breast milk, the drug should be used with caution in nursing women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The following frequency terminology is used:

- Very common: ≥ 1/10;
- Common: ≥ 1/100, < 1/10;
- Uncommon: ≥ 1/1,000, < 1/100;
- Rare: ≥ 1/10,000, < 1/1,000;
- Very rare: < 1/10,000;
- Not known (cannot be estimated from the available data)

Immune system disorders

Very rare: Allergic reactions (urticaria, rhinitis, dyspnoea, Quincke's oedema), anaphylactic shock

Nervous system disorders

Common: Dizziness, headache
Uncommon: Tremor, sweating
Rare: Seizures, tension

Seizures have occurred rarely following administration of naloxone hydrochloride; however, a causal relationship to the drug has not been established. Higher than recommended dosage in postoperative use can lead to tension.

Cardiac disorders

Common: Tachycardia
Uncommon: Arrhythmia, bradycardia
Very rare: Fibrillation, cardiac arrest

Vascular disorders
Common: Hypotension, hypertension
Hypotension, hypertension and cardiac arrhythmia (including ventricular tachycardia and fibrillation) have also occurred with the postoperative use of naloxone hydrochloride. Adverse cardiovascular effects have occurred most frequently in postoperative patients with a pre-existing cardiovascular disease or in those receiving other drugs that produce similar adverse cardiovascular effects.

Respiratory, thoracic and mediastinal disorders
Very rare: Pulmonary oedema
Pulmonary oedema has also occurred with the postoperative use of naloxone hydrochloride.

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting
Uncommon: Diarrhoea, dry mouth
Nausea and vomiting have been reported in postoperative patients who have received doses higher than recommended. However, a causal relationship has not been established, and the symptoms may be signs of too rapid antagonisation of the opioid effect.

Skin and subcutaneous tissue disorders
Very rare: Erythema multiforme
One case of erythema multiforme cleared promptly after naloxone hydrochloride was discontinued.

General disorders and administration site conditions
Common: Postoperative pain
Uncommon: Hyperventilation, irritation of vessel wall (after i.v. administration); local irritation and inflammation (after i.m. administration)
Higher than recommended dosage in postoperative use can lead to the return of pain.
A fast reversal of opioid effect can induce hyperventilation.

4.9 Overdose
There have been no reports of acute overdosage due to naloxone hydrochloride.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antidotes
ATC code: V03AB15
Naloxone hydrochloride is a semisynthetic (N-allylnoroxymorphine hydrochloride) opioid antagonist which is derived from thebaine. When administered in usual doses to patients who have not recently received opioids, naloxone exerts little or no pharmacologic effect. Even extremely high doses of the drug (10 times the usual therapeutic dose) produces insignificant
analgesia, only slight drowsiness and no respiratory depression, psychotomimetic effects, circulatory changes or miosis.

In patients who have received large doses of diamorphine or other analgesic drugs with morphine-like effects, naloxone antagonises most of the effects of the opioid. There is an increase in respiratory rate and minute volume, arterial \( p \) CO\(_2\) decreases toward normal and blood pressure returns to normal if depressed. Naloxone antagonises mild respiratory depression cause by small doses of opioids. Because the duration of action of naloxone is generally shorter than that of the opioid, the effects of the opioid may return as the effects of naloxone dissipates. Naloxone antagonises opioid-induced sedation or sleep. Reports are conflicting on whether or not the drug modifies opioid-induced excitement or seizures.

Naloxone does not produce tolerance or physical or psychological dependence. However, 0.4 mg of naloxone hydrochloride administered SC will precipitate potentially severe withdrawal symptoms in patients physically dependent on opioids or pentazocine. The precise mechanism of action of the opioid antagonist effects of naloxone is not known. Naloxone is thought to act as a competitive antagonist at \( \mu \), K or \( \sigma \) opioid receptors in the central nervous system. It is thought that the drug has the highest affinity for the \( \mu \) receptor.

5.2 Pharmacokinetic properties

Naloxone has an onset of action within 1 to 2 minutes following IV administration and within 2 to 5 minutes following SC or IM administration. The duration of action depends on the dose and route of administration and is more prolonged following IM administration than after IV administration. In one study, the duration of action was 45 minutes following IV administration of naloxone hydrochloride 0.4 mg/70 kg.

Following administration of 35 or 70 micrograms of naloxone hydrochloride in the umbilical vein in neonates in one study, peak plasma naloxone concentrations occurred within 40 minutes and were 4 - 5.4 ng/ml and 9.2 - 20.2 ng/ml, respectively. After IM administration of 0.2 mg to neonates in the same study, peak plasma naloxone concentrations of 11.3 - 34.7 ng/ml occurred within 0.5 - 2 hours.

Following parenteral administration, naloxone is rapidly distributed into body tissues and fluids. In rats, high concentrations are observed in the brain, kidney, spleen, lungs, heart and skeletal muscles. In humans, the drug readily crosses the placenta. It is not known whether naloxone is distributed into milk.

The plasma half-life of naloxone has been reported to be 60 to 90 minutes in adults and about 3 hours in neonates.

Naloxone is rapidly metabolised in the liver, principally by conjugation with glucuronic acid. The major metabolite is naloxone-3-glucuronide. Naloxone also undergoes N-dealkylation and reduction of the 6-keto group followed by conjugation. Limited studies with radiolabeled naloxone indicated that 25 -
40% IV doses of the drug is excreted as metabolites in urine in 6 hours, about 50% in 24 hours and 60 - 70% in 72 hours.

5.3 Preclinical safety data
Not applicable since naloxone has been used in clinical practice for many years and its effects in man are well known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Chloride
Sodium Hydroxide (for pH-adjustment)
Hydrochloric Acid (for pH-adjustment)
Water for Injection

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
3 years
Shelf life after first opening :
After first opening the medicinal product should be used immediately.

Shelf-life after dilution :
Chemical and physical in-use stability has been demonstrated for 48 hours below 20°C.

From the 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 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Store the ampoule in the outer carton until used to protect from light. Please refer to section 6.3 for storage of the product that have been diluted.

6.5 Nature and contents of container
The product is contained in a glass ampoule (Type I) of 1ml.
In boxes of 10 ampoules.

6.6 Special precautions for disposal
Naloxone may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of naloxone in 500 ml of either solution provides a concentration of 4 micrograms /ml. Infusion should be commenced as soon as practicable after preparation of the mixture in order to reduce microbiological hazards.. The rate of administration should be titrated in accordance with the patient's response. Parenteral drug products should be
inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
UKR Regulatory Affairs Ltd.
The Bull Pen, Home Farm, Banbury Road
Caversfield, Nr Bicester, OX27 8TG

8 MARKETING AUTHORISATION NUMBER(S)
PL 19364 / 0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/02/2011

10 DATE OF REVISION OF THE TEXT
18/02/2011
PATIENT INFORMATION LEAFLET

NALOXONE HYDROCHLORIDE
400 MICROGRAMS/ML
solution for injection

Read all of this leaflet carefully before you start using this medicine
- Keep this leaflet. You may need to read it again
- If you have further questions, please ask your doctor or your pharmacist
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Naloxone injection is and what it is used for
2. Before you are given Naloxone injection
3. How Naloxone injection is given
4. Possible side effects
5. Storing Naloxone injection
6. Further information

1. WHAT NALOXONE IS AND WHAT IT IS USED FOR
Naloxone belongs to a group of medicines known as opioid antagonists. It is used to treat very shallow breathing that may be caused by opioid pain killers. It may also be used to diagnose opioid overdose.

2. BEFORE YOU ARE GIVEN NALOXONE INJECTION
Naloxone injection must not be administered if you are hypersensitive (allergic) to Naloxone or any of the other ingredients of Naloxone injection.
Please note:
You should let your doctor know if you are dependent on opioid painkillers such as diamorphine (heroin), even if you are being treated with methadone, as naloxone may cause withdrawal symptoms.
Take special care with Naloxone injection and tell your doctor if your:
- have problems with your heart or circulation,
- are in pain,
- have recently been given a large dose of opioid painkillers,
- are physically dependent on opioids and that are pregnant, planning pregnancy or breast-feeding,
- are taking medicines that may affect your heart function,
- have just had an operation.

Taking other medicines
Naloxone may interfere with the actions of other medicines. These include:
- Opioid or opioid-like painkillers, such as pentazocine and fentanyl
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Inform your doctor if you are breast-feeding.

Driving and using machines
You should not drive or operate machinery until you have fully recovered from the effects of Naloxone injection.

Important information about some of the ingredients of Naloxone injection:
Each ampoule contains 3.5 mg (0.154 mmol) of sodium.

3. HOW NALOXONE 400 MICROGRAMS/ML SOLUTION FOR INJECTION IS GIVEN
Dosage: Your doctor will decide the dose that is best for you. The dose administered will be dependent on what symptoms you present and where the injection is given.

Methods of Administration: A nurse or doctor will give you an injection. The injection may be given into the muscle, vein or skin.

The following information is intended for medical or healthcare professionals only:

Drug name:

NALOXONE HYDROCHLORIDE
400 MICROGRAMS/ML
solution for injection

Safety Information:
Solution for injection.

Incompatibilities:
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
If you receive more Naloxone 400 micrograms/ml Solution for injection than you should: Please consult your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Naloxone Hydrochloride 400 micrograms/ml solution for injection can cause side effects, although not everybody gets them.
The frequency of side effects is classified into the following categories: Very common In more than 1 in 10 patients.
Common In more than 1 in 100 patients.
Uncommon In more than 1 in 1,000 patients, but less than 1 in 100 patients.
Rare In more than 1 in 10,000 patients, but less than 1 in 1,000 patients.
Very rare In less than 1 in 10,000 patients, including isolated reports

It may be difficult to know what side effects Naloxone Hydrochloride 400 micrograms/ml solution for injection has, because it is always given after other drugs have also been used.

Immune system disorders: Very rare: Allergic reactions (rash, nasal stuffiness or a cold, difficulty breathing, Quinke’s oedema (facial swelling), allergic shock.

Nervous system disorders: Common: Dizziness, headache.

Cardiac disorders: Common: Fast heart beat.


Gastrointestinal disorders: Very common: Nausea.

Skin and subcutaneous tissue disorders: Very rare: Discoloration and lesions of the skin (erythema multiforme).

General disorders and administration site conditions:

- Common: If too large a dose is given after an operation, you may become excited and feel pain (because the paralyzing effects of the medicine you were given will have been counteracted as well as the effects on your breathing).

- Uncommon: Over breathing (hyperventilation), irritability of the blood vessel wall has been reported after i.v. administration, local irritation and inflammation have been reported after i.m. administration.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NALOXONE 400 MICROGRAMS/ML SOLUTION FOR INJECTION
Keep out of the reach and sight of children.
Expiration date: Do not use after the expiry date stated on the ampoule. The expiry date refers to the last day of the month.
Storage conditions: Store in the original package.
Store the ampoule in the outer carton until used to protect from light.
Store diluted solutions below 20°C.

Medicines should not be disposed of via wastewater or household waste. Ask your doctor or pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Naloxone 400 micrograms/ml Solution for injection contains:
The active substance is Naloxone hydrochloride. Each 1 ml ampoule contains 400 micrograms Naloxone hydrochloride as dihydrate, equivalent to 400 micrograms Naloxone hydrochloride. The other ingredients are sodium chloride, water for injection, sodium hydroxide or hydrochloric acid (for pH adjustment).

What Naloxone 400 micrograms/ml Solution for injection looks like and contents of the pack:
Your medicinal product is a clear and colourless solution in clear glass ampoule containing 1 ml solution for injection. Boxes of 10 ampoules.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

Manufacturing Authority Holder: UKR Regulatory Affairs Limited
The Bull Pan, Home Farm, Boxbury Road
Caversfield, Nr Bicester, OX27 8TG

Manufacturer: Laboratoire Agnati
1, rue Alexandre Fleming
69007 LYON - France

This leaflet was last approved in January 2010.

Instructions on preparation and dilution:
Naloxone may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of naloxone in 500 ml of either solution provides a concentration of 4 micrograms/ml. Infusion should be commenced as soon as practicable after preparation of the mixture in order to reduce microbiological hazards. The rate of administration should be titrated in accordance with the patient’s response. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Administration:
It depends how much is needed to reverse the effects on respiratory depression. The following is a guide.

For adults:
• To treat an overdose or suspected overdose of opioids, between 400 and 2000 micrograms may be given every 1-2 minutes.
• After an operation 100-200 micrograms may be given every 2-3 minutes.

Naloxone is always given by injection by a doctor or health professional, usually into a blood vessel. It may be given slowly through a drip. It can be given into a muscle or under the skin.

For children:
• The usual dose is 10 micrograms for every kg they weigh increased to 100 micrograms per kg if there is not a good enough response.

Patients are monitored to make sure the effect of the naloxone lasts as long as the drugs it is counteracting. Additional doses may be given every 1-2 hours if necessary.

Storage and Shelf Life:
Store the ampoule in the outer carton until used to protect from light.
Shelf life: 3 years

Shelf life after first opening: The medicinal product should be used immediately.

Shelf life after dilution: Chemical and physical in-use stability has been demonstrated for 48 hours below 20°C.

From the microbiological point of view, the dilutions 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 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
LABELLING

Label

Naloxone Hydrochloride 400 mcg/ml Solution for injection
For IV, IM, SC injection, or IV infusion
1 ml
PL19364/0031
Batch:
EXP.:
Carton

Composition:
Naloxone hydrochloride (as dihydrate) 440mcg/ml. Equivalent to
400mcg/ml naloxone hydrochloride.
Also contains: sodium chloride, sodium hydroxide, hydrochloric acid,
water for injections.
See leaflet for further information.
Solution for injection, 1ml glass ampoule in box of 10.
Read the package leaflet before use. For intravenous (IV),
intra muscular (IM), subcutaneous (SC) use, or IV infusion.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store the ampoule in the outer carton until used to protect from
light.
Visually inspect for particulate matter and discoloration prior to
administration.
After opening: the product should be used immediately.
After dilution: chemical and physical in-use stability has been
demonstrated for 48 hours below 20°C. From the microbiological
point of view, the product should be used immediately. If not sent
immediately, in use storage times and conditions prior to use are the
responsibility of the user and would normally not be longer than 24
hours at 2-8°C. Unless dilution has taken place in controlled and
validated aseptic conditions.

Naloxone Hydrochloride
400 mcg/ml SOLUTION FOR INJECTION

Route: IV, IM or SC

10 ampoules
400 mcg
1 ml

MHRA PAR; NALOXONE HYDROCHLORIDE 400 MICROGRAMS/ML SOLUTION FOR
INJECTION, PL 19364/0031