IN USE PRODUCT SAFETY ASSESSMENT REPORT: NALOXONE PRODUCTS FOR EMERGENCY OPIATE REVERSAL IN NON-MEDICAL SETTINGS

SUMMARY OF ASSESSMENT AND ITS FINDINGS

BACKGROUND

Naloxone is an opiate antagonist; one of its uses is reversal of opiate toxicity in emergency situations when there is immediate threat to life or a diagnosis of respiratory depression (1,2). When used in an emergency, naloxone may be used by anyone for the purpose of saving a life; it is now also exempt from prescription only medicines requirements when supplied by a drug service commissioned by the NHS, a local authority or Public Health Agency (2,3). Naloxone should therefore be widely available for anyone needing access to it for the purpose of saving a life.

Naloxone is recommended and supplied across England in 'take-home naloxone' programmes to opiate misusers who are at potential risk of overdose and to carers, family or friends liable to witness an overdose (known as 'non-medical responders'). This enables non-medical responders to respond in the event of an emergency overdose (3). Thus it is essential that suitable products are available at the point of use. Naloxone is available in two presentations in the UK: as ampoules and as prefilled syringes. There is an inherent risk associated with the use of ampoules in a non-medical setting as they require greater manipulation than prefilled syringes before they are ready-to-use. Public Health England advises that prefilled syringes are simpler for emergency use by non-medical responders (3). As such, prefilled syringes are considered the presentation of choice for 'take-home naloxone' programmes, although ampoules may be an option depending on local circumstances.

This UKMi assessment reviews the four UK licensed naloxone products available in a prefilled syringe preparation and summarises considerations associated with their in-use safety when used as an emergency antidote in a non-medical setting.

DETAILS OF PRODUCT (S) ASSESSED

The products assessed using the validated UKMi product assessment tool were:

1. Prenoxad® (naloxone hydrochloride) 1mg/mL solution for injection in a prefilled syringe (2mL); Martindale Pharmaceuticals Ltd
2. Naloxone Hydrochloride Injection 1mg/mL solution for injection in a prefilled syringe (2mL); Martindale Pharmaceuticals Ltd
3. Naloxone Hydrochloride Injection, 400 micrograms/mL solution for injection in a Minijet prefilled syringe (1mL); International Medication Systems (UK) Ltd #
4. Naloxone Hydrochloride Injection, 400micrograms/mL solution for injection in a Minijet prefilled syringe (2mL); International Medication Systems (UK) Ltd#

Assessments were carried out with reference to: dummy versions of the products and high resolution images supplied by the manufacturers; summaries of product characteristics (SmPC) and packaging inserts (4-9); and additional training and educational materials supplied by Martindale Pharmaceuticals (10-12). The assessment process is summarised at the end of the report (page 5).

The manufacturers are in the process of divesting the product licence

CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL

Prefilled syringes are the preferred formulation choice for 'take-home naloxone' programmes and four naloxone products are available in this presentation in the UK. However, some risks will be associated with the use of these products in a non-medical setting and safe use will require careful consideration of the risk associated with each available product. Product features and their risks are summarised below; mitigating and other necessary actions are considered in the next section.

Table 1: Naloxone prefilled syringe products available in the UK

Product (manufacturer)	Summary of product licence	Total amount of naloxone available	Device details and disposables supplied with product	Manufacturer product information
Prenoxad® (naloxone hydrochloride) 1mg/mL solution for injection in a prefilled syringe, 2mL (Martindale Pharmaceuticals Ltd)	Reversal of opioid induced respiratory depression; indicated for use in the home, non-medical setting or in a health facility setting.	2mg	Luer lock connector. Pack contains two 23G x 1¼ inch needles.	SmPC Packaging insert Risk Management Programme: www.prenoxadinjection.com
Naloxone Hydrochloride Injection 1mg/mL solution for injection in a prefilled syringe, 2mL (Martindale Pharmaceuticals Ltd)	Reversal of opioid induced respiratory depression. Setting for use not specified.	2mg	Luer lock connector	SmPC Packaging insert
Naloxone Hydrochloride Injection, 400micrograms/mL solution for injection in a Minijet prefilled syringe, 1mL (International Medication Systems UK Ltd)	Treatment of opioid induced respiratory depression. Setting for use not specified.	400mcg	Luer lock connector	SmPC Packaging insert
Naloxone Hydrochloride Injection, 400micrograms/mL solution for injection in a Minijet prefilled syringe 2mL (International Medication Systems UK Ltd)	Treatment of opioid induced respiratory depression. Setting for use not specified.	800mcg	Attached 1¼ inch stainless steel needle	SmPC Packaging insert

Cost of products range between £15-20 per syringe (1)

Drug treatment services should consider the following when choosing the most appropriate product to supply in 'take-home naloxone' programmes:

Licensing status

- All naloxone prefilled syringe products are licensed for the reversal/treatment of opioid induced respiratory depression.
- Prenoxad® was specifically developed for use in community and as such the product licence specifies it can be used in the home, non-medical setting or in a health facility setting by appropriate individuals which may include a non-medical responder. The product licences for the three non-proprietary products do not indicate use for a specific setting or user.

Suitability of naloxone products to safely deliver dosing in non-medical settings

- A relatively low first dose of naloxone (*typically 400 micrograms*) is recommended for the emergency treatment of acute opioid overdose associated with drug misuse and dependence. Subsequently, this initial dose can be followed up with further low doses as long as needed to achieve and maintain the overdose blocking effects (1,3,13). Currently there is no clear guidance on how much naloxone should be carried by non-medical responders to cover all likely doses (14). For further information on naloxone dosing see UKMi Q&A (15) What naloxone doses should be used in adults to reverse urgently the effect of opioids or opiates?
- Each of the four products are presented differently. The **non-proprietary naloxone 1mg/mL** (Martindale) and **Prenoxad® 1mg/mL** preparations are labelled with 5 individual marked doses (*of 400micrograms*) enabling graduated administration of low doses of naloxone. The **non-proprietary naloxone 400micrograms/mL** (IMS UK Ltd) preparations contain a total dose of 400 micrograms in the 1mL preparation (graduated in 100 micrograms steps) and 800 micrograms in the 2mL preparation (graduated in 200 micrograms steps). These two products enable administration of the initial recommended dose(s) but access to further products would be required for subsequent follow-up doses.
- The **Prenoxad® 1mg/mL** presentation specifically supports use in the community: the outer product packaging is labelled with dosing instructions "inject 0.4mL (400micrograms) into the outer thigh muscle or upper arm muscle. If no response repeat at 2-3 minute intervals" and the prefilled syringe is labelled with "1 dose, 2 dose, 3 dose" etc. In our view, the variations in labelled instructions between the outer packaging (0.4mL) and prefilled syringe (1 dose) may be a potential source of confusion for non-medical responders. The **non-proprietary naloxone 1mg/mL** (Martindale) prefilled syringe is labelled with incremental doses in volume only (0.4mL steps). Both the **non-proprietary naloxone 400micrograms/mL** (IMS UK Ltd) syringes are labelled with incremental doses in strength and volume (steps of 100 micrograms/0.25mL or 200 micrograms/0.5mL). The labelling and lack of clear administration instructions on the outer product packaging of the three non-proprietary products may be a potential source of confusion for non-medical responders with regards to the correct dose to administer.
- The intramuscular (IM) route in the most suitable route for naloxone administration in the community (14). The **2mL non-proprietary naloxone 400 micrograms/mL** (IMS UK Ltd) preparation is provided with an attached needle ready for IM use in emergency situations. The **Prenoxad®** preparation is available as a kit containing two needles which are suitable for IM use (16), but some manipulation will be required to attach the needle to the product. The **non-proprietary naloxone 1mg/mL** (Martindale) and the **1mL non-proprietary naloxone 400 micrograms/mL** (IMS UK Ltd) products are not supplied with needles but are compatible with standard 'luer lock' needles suitable for IM use (typically 19-25 gauge) (16,17,18). For the products not completely 'ready-to-use', there is a risk of delayed naloxone administration.

Potential risk of wrong dose administration

- The **non-proprietary naloxone 1mg/mL** (Martindale) and **Prenoxad® 1mg/mL** preparations enable graduated administration of low doses of naloxone. However, as both products contain a total of 2mg naloxone, there is a risk of the full 2mg being administered initially and not incrementally in low doses as recommended. This may be a particular risk as products will be used by non-medical responders. The **naloxone 400 micrograms/mL** products contain a total of 400 micrograms (1mL) or 800 micrograms (2mL) of naloxone and therefore the same risk of overdose is not present with these products.
- The risk of wrong dose administration is compounded by the fact that there are four available products of various strengths and total amount, and confusion between them is possible. This is a particular risk if there is familiarity with naloxone products of a specific strength, and/or if training has been focused on administration in volume rather than dose.
- The clinical issues associated with accidental overdose of naloxone are beyond the scope of this paper;

however, initial doses above 800 micrograms are more likely to precipitate significant withdrawal symptoms. It is recommended that naloxone should be given in a careful, graduated approach to reduce the possibility of unnecessary adverse effects. (2,3,14) See UKMi document for further discussion on naloxone administration in drug misuse and dependence.

Information supplied with the products

- All products are provided with information to support use; this includes packaging inserts intended for the user and summaries of product characteristics for prescribers. Martindale Pharmaceuticals Ltd has produced a dedicated website as part of the Risk Management Programme for **Prenoxad®** which contains a suite of approved product information and training material for patients, prescribers and pharmacists, specifically designed to support use in the non-medical setting. These are available here http://www.prenoxadinjection.com .

POTENTIAL NEXT STEPS AND MITIGATION ACTIONS

The following potential next steps and mitigation actions can be considered by drug treatment services to ensure safe use of products in 'take-home naloxone' programmes:

1. **Product choice to safely deliver naloxone dosing in a non-medical setting**
   - It is vital that naloxone products supplied are suitable for the non-medical setting; in our view prefilled syringes are the preferred formulation choice compared to vials or ampoules.
   - Each of the four prefilled syringe products are presented differently and thus features of each should be considered carefully.
     - The setting for use is not specified for the three non-proprietary products. Martindale Pharmaceuticals Limited markets two products of the same strength, one licenced for use in a non-medical setting, **Prenoxad®,** and one that is not, the **non-proprietary naloxone 1mg/mL** product**.** Clearly **Prenoxad®** is the more appropriate product from the two for 'take-home naloxone' programmes.
     - Products chosen for supply must support delivery of the recommended low incremental doses of naloxone. All four products enable administration of the initial recommended dose(s) but access to further products would be required for subsequent follow-up doses when using either of the **non-proprietary naloxone 400micrograms/mL** (IMS UK Ltd) preparations.
     - Products supplied should minimise the risk of inappropriate dose administration. The **Prenoxad®** presentation specifically supports use in a non-medical setting with dosage instructions on the outer and inner product packaging but a risk of inadvertent administration of the full syringe contents is possible. The same risk is not present with the **naloxone 400 micrograms/mL** (IMS UK Ltd) products. See training programmes (below) for mitigating actions.
     - Tailored information material suitable for non-medical responders should be available for products supplied. For **Prenoxad®**, the manufacturer supplies regulatory approved training material supporting use in the non-medical setting; for the other products suitable material should be produced locally.
     - Minimal manipulation is desirable for products administered in the non-medical setting. The **2mL non-proprietary naloxone 400 micrograms /mL** (IMS UK Ltd) preparation is "ready-to-administer"; the other three products require the user to attach the needle to the syringe. Local supply of appropriate luer lock needles suitable for IM use will be necessary for the **non-proprietary naloxone 1mg/mL** (Martindale) and **1mL non-proprietary naloxone 400 micrograms/mL** (IMS UK Ltd) products; the logistics of adding additional ancillaries to product kits should be considered.
2. **Training programmes**

   Suitable training and advice for families, carers and peers is vital to support safe administration of naloxone products. Training should be provided on the specific product selected for supply locally; training on assembly and product use is essential. A key element of the training will include advice on administering naloxone in

small graduated doses. See Public Health England guidance for further information on 'what to cover in overdose and naloxone training'.

3. **Safe use of available products across local areas**
   Due to the differences between the available products, continuity of products across local areas may be useful to implement in order to mitigate the risk of administration errors, particularly those related to unfamiliarity with products. Co-ordination between individual drug treatment services in the locality would be required.
4. **Record of supply and storage**
   Naloxone is exempt from prescription only medicines requirements when supplied by a drug service commissioned by the NHS, a local authority or Public Health Agency but it is good practice to develop appropriate mechanisms to record product supply; details of products supplied and their expiry dates should be documented. There should be systems in place which flag approaching expiry dates of products to keyworkers/organisations for re-supply. (2) Advice on safe storage and safe disposal following use should also be given to organisations/individuals who are supplied products.
5. **Local protocols**
   The strategies suggested above should be reflected in local protocols, including details on product choice, information to be supplied with products, training programmes, and mechanisms for monitoring and record keeping of product supply. (2) Refer to Public Health England guidance for further information on introducing 'take-home naloxone' programmes.

This report was produced in March 2016 using dummy products and photographic images of products available at the time of assessment. Images were obtained primarily from pharmaceutical companies, but also from the Commercial Medicines' Unit PharmaQC database (http://cmu.dh.gov.uk/medicines/pharmaqc-database/) and from various sources within the NHS.

This report summarises product assessments undertaken by: London Medicines Information Service (Northwick Park Hospital) and South West Medicines Information and Training. We are also grateful for the input of clinical specialists in Drug Misuse and Dependence in completing this piece of work. For comments email lnwh-tr.medinfo@nhs.net.

The UKMI product safety assessment group would appreciate your views on the usefulness of this report. We have devised a short survey which we would appreciate you completing, it should take approximately 10 minutes to complete. Click the following link to complete the survey:
https://www.surveymonkey.com/r/UKMiProductSafetyAssessments.

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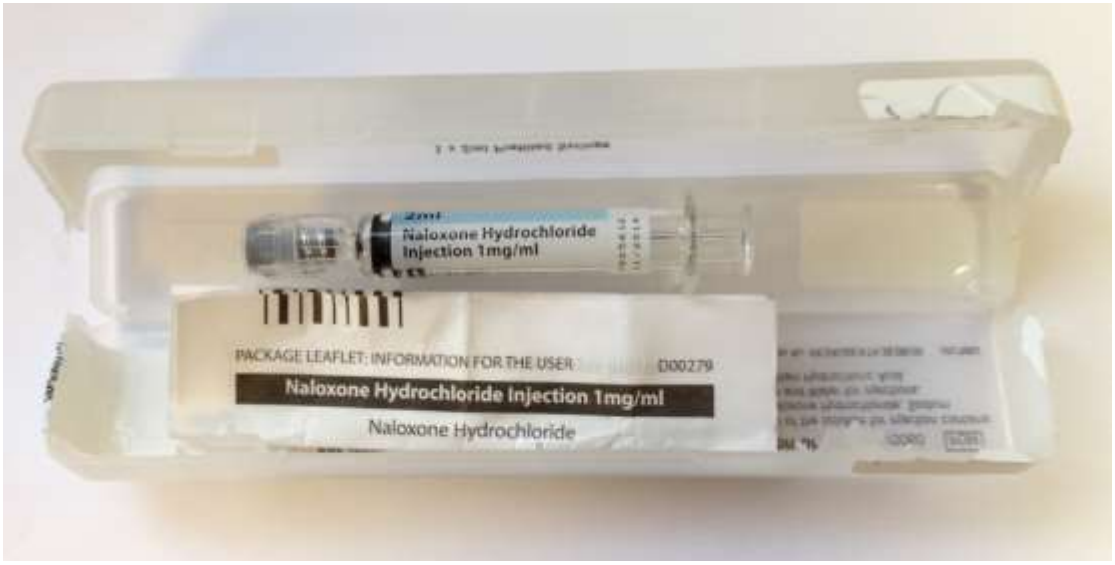
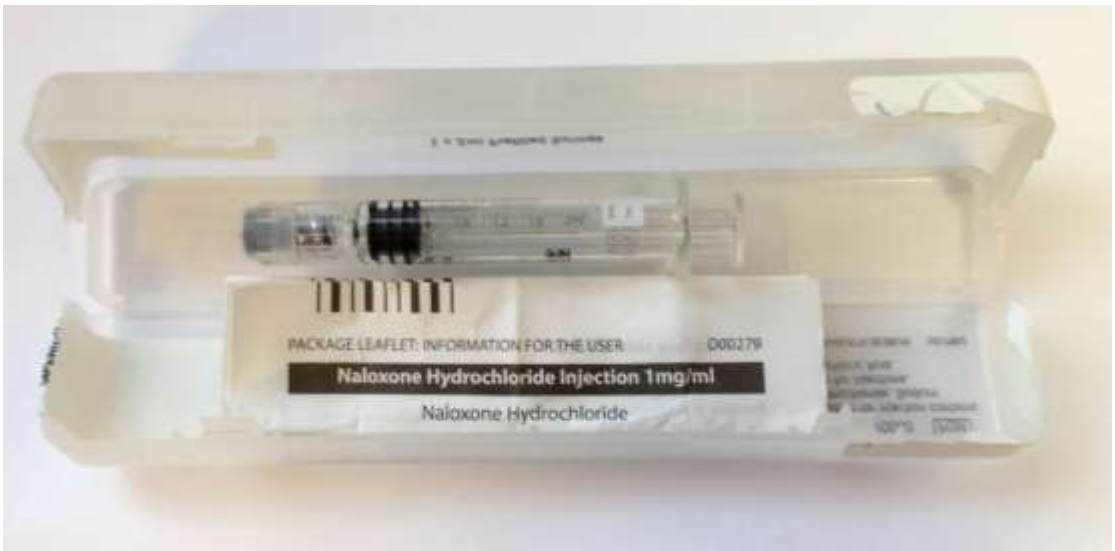
PRODUCT PHOTOS

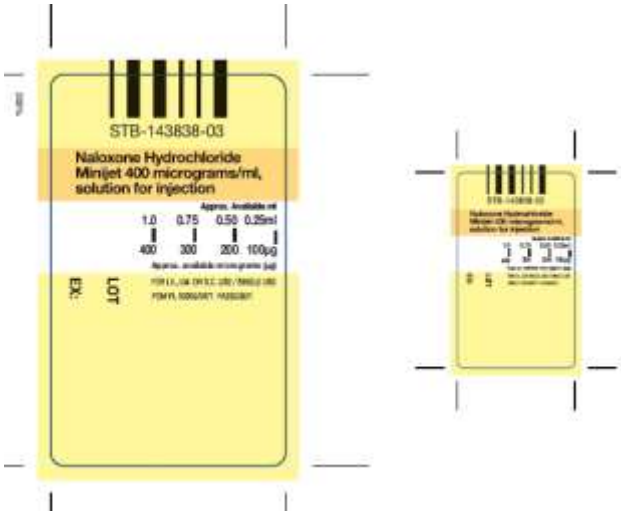
Prenoxad® (naloxone) 1mg/ml prefilled syringe (Martindale Pharmaceuticals Ltd)

Naloxone 1mg/ml prefilled syringe (Martindale Pharmaceuticals Ltd)





Naloxone Hydrochloride Injection 400mcg/ml solution (1mL) Minijet prefilled syringe (International Medication Systems UK Ltd)



Naloxone Hydrochloride Injection 400mcg/ml solution (2mL) Minijet prefilled syringe (International Medication Systems UK Ltd)