PRENOXAD 1MG/ML INJECTION

PL 12064/0125

UKPAR

TABLE OF CONTENTS

Lay Summary ........................................ Page 2
Scientific discussion ............................... Page 3
Steps taken for assessment ....................... Page 10
Steps taken after authorisation .................. Page 11
Summary of Product Characteristics .......... Page 24
Product Information Leaflet ..................... Page 25
Labelling ............................................. Page 26
On 29th June 2012, the MHRA granted Aurum Pharmaceuticals Limited a Marketing Authorisation (licence) for Prenoxad 1mg/ml Injection (which at that time had the name Naloxone Hydrochloride 1 mg/ml Injection).

Prenoxad 1mg/ml Injection contains the active ingredient naloxone hydrochloride.

Naloxone belongs to a group of medicines that reverse the action of opioid drugs e.g. morphine.

Prenoxad 1mg/ml Injection is used to:
- Reverse the action of opioid drugs e.g. if an overdose of these drugs has been taken.
- Reverse the action of opioids given during surgery.
- Allow a newborn baby to breathe following birth if opioids have been given to the mother during childbirth.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Prenoxad 1mg/ml Injection outweigh the risks; hence a Marketing Authorisation has been granted.
PRENOXAD 1MG/ML INJECTION

PL 12064/0125

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Non-clinical assessment Page 7
Clinical assessment (including statistical assessment) Page 8
Overall conclusions and risk benefit assessment Page 9
INTRODUCTION

The MHRA granted a Marketing Authorisation for the medicinal product Prenoxad 1mg/ml Injection (PL 12064/0125) to Aurum Pharmaceuticals Limited on 29th June 2012. This prescription-only medicine (POM) is indicated:

- 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.

- The diagnosis of suspected acute opioid overdosage.

- To counteract respiratory and other CNS depression in the new-born resulting from the administration of analgesics to the mother during childbirth.

This application for Prenoxad 1mg/ml Injection is submitted according to Article 10c (informed consent application) of Directive 2001/83/EC, as amended, cross-referring to Naloxone Hydrochloride Injection 1 mg/ml, licensed to Aurum Pharmaceuticals Limited on 10th July 2000 (PL 12064/0060).

It is considered that 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 together with the necessary means for notification of any adverse reaction suspected of occurring.

A satisfactory justification was provided for the absence of a Risk Management Plan.

No new data were submitted nor were they necessary for this “informed consent” application, as the data are identical to that of the previously granted cross-reference product.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 12064/0125
PROPRIETARY NAME: Prenoxad 1mg/ml Injection
ACTIVE(S): Naloxone hydrochloride
COMPANY NAME: Aurum Pharmaceuticals Limited
E.C. ARTICLE: Article 10c of Directive 2001/83/EC, as amended
LEGAL STATUS: POM

1. INTRODUCTION
This is an “informed consent” application for Prenoxad 1mg/ml Injection (PL 12064/0125) submitted under Article 10c of Directive 2001/83/EC, as amended. The proposed Marketing Authorisation Holder (MAH) is Aurum Pharmaceuticals Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG.

This application cross-refers to Naloxone Hydrochloride Injection 1 mg/ml, licensed to Aurum Pharmaceuticals Limited on 10th July 2000 (PL 12064/0060).

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 NAME(S)
The product has been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The product contains 1 mg naloxone hydrochloride per 1 ml of solution. The product is a sterile, clear and colourless solution for injection/infusion in a pre-filled syringe. Prenoxad 1mg/ml Injection is for intravenous, intramuscular or subcutaneous injection or intravenous infusion.

The product is packaged in a glass (Type I) 2 ml pre-filled syringe. One syringe is contained in a box.

The shelf-life is 3 years with storage conditions ‘Do not store above 25°C’ and ‘Store in the original container.’

This is consistent with the details registered for the cross-reference product.

2.3 Legal status
Prescription-only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Aurum Pharmaceuticals Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG. The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The composition is consistent with the details registered for the cross-reference product.
2.7 Manufacturing process
The manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The finished product specification is in-line with the details registered for the cross-reference product. A commitment has been provided to update the finished product specification for the proposed and reference product in-line with The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance.

2.9 Drug substance specification
The drug substance specification is consistent with the details registered for the cross-reference product. A commitment has been provided to update the drug substance specification in-line with the European Pharmacopoeia monograph for naloxone hydrochloride.

2.10 TSE Compliance
None of the excipients used contain material of animal or human origin. This information is consistent with the cross-reference product.

3. EXPERT REPORTS
Quality, non-clinical and clinical expert statements have been provided in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The SmPC is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET (PIL)/LABELLING
PIL
The PIL readability has cross-referred to the reference product PIL readability, which is acceptable since the content, layout, formatting and appearance of the test leaflet are identical to that of the reference PIL.

Labelling
The artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements.

7. CONCLUSIONS
The data submitted with the application are acceptable. The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with this application and none are required for an application of this type.

A satisfactory justification was provided for the absence of an Environmental Risk Assessment.
CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for this application are consistent with those previously approved for the cross-reference product and, as such, has been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
This application is considered a duplicate of the previously granted application, Naloxone Hydrochloride Injection 1 mg/ml, licensed to Aurum Pharmaceuticals Limited on 10th July 2000 (PL 12064/0060).

No new or unexpected safety concerns arise from this application.

At the time of assessment, the SmPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product.

Extensive clinical experience with naloxone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk:benefit is, therefore, considered to be positive.
STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Application on 1(^{st}) December 2011.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 26(^{th}) January 2012.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application further information was requested regarding the quality section of the dossier on 27(^{th}) January 2012 and 11(^{th}) May 2012.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 30(^{th}) March 2012 and 15(^{th}) June 2012 for the quality section.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 29(^{th}) June 2012.</td>
</tr>
</tbody>
</table>
## STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Description</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/07/2012</td>
<td>Type II variation</td>
<td>To update sections 1, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 6.1, 6.5 and 6.6 of the SmPC to change the presentation and method of use of the finished product to make the product suitable for use in a community setting (i.e. to be administered by people who are not healthcare professionals). Changes relating to community use of the product are also made to the PIL and labels.</td>
<td>Variation granted 11/12/2012</td>
</tr>
</tbody>
</table>
ANNEX 1 – VARIATION ASSESSMENT REPORTS

PHARMACEUTICAL VARIATION ASSESSMENT REPORT

Reason:
To update sections 1, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 6.1, 6.5 and 6.6 of the SmPC to change the presentation and method of use of the finished product to make the product suitable for use in a community setting (i.e. to be administered by people who are not healthcare professionals). Changes relating to community use of the product are also made to the PIL and labels.

Supporting evidence:
- Application form and attachment
- Relevant pages of variation guidelines
- Updated sections of the dossier, including the Clinical Overview
- Proof of payment

Evaluation:
This variation application concerns a change in the presentation and method of use of a currently authorised product to create a medicinal product that can be used in the community by opioid misusers in order to reverse respiratory depression due to known or suspected opiate overdose whilst specialist attention is obtained.

The Marketing Authorisation Holder (MAH) proposes to make changes to the product SmPC, Patient Information Leaflet, labels and container closure system. It should be noted that the MAH has been requested to make a product that is suitable for administration by people who are not healthcare professionals commercially available under a Marketing Authorisation by several healthcare bodies, including NHS Scotland. The medicinal product has been supplied as an unlicensed product by the Scottish Health Boards under a Patient Group Directive.

Conclusion:
The updates to the SmPC, Patient Information Leaflet and product labels are satisfactory.

The previously approved product name, Naloxone Hydrochloride 1 mg/ml Injection, is similar to the name of another product that is not meant to be administered by people who are not healthcare professionals. In order to avoid the two products being confused, leading to a potential safety issue, the product name was changed to Prenoxad 1mg/ml Injection.

Prenoxad 1mg/ml Injection is a sterile solution for injection presented in a glass (Type I) 2ml prefilled syringe. The pack contains two 23G x 1¼” needles. Suitable modifications have been made to the product packaging to make it suitable for use by non healthcare professions in the community.

The proposed variation is pharmaceutically acceptable.
CLINICAL VARIATION ASSESSMENT REPORT

Reason:
To update sections 1, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 6.1, 6.5 and 6.6 of the SmPC to change the presentation and method of use of the finished product to make the product suitable for use in a community setting (i.e. to be administered by people who are not healthcare professionals). Changes relating to community use of the product are also made to the PIL and labels.

Background:
Prenoxad 1mg/ml Injection is approved in the United Kingdom under Marketing Authorisation PL 12064/00125 as a prescription-only medicine intended for use by healthcare professionals. The product is currently indicated 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) whether accidental or as a result of abuse or illegal use of opiates. It may also be used for the diagnosis of suspected acute opioid overdosage. Naloxone may also be used to counteract respiratory and other CNS depression in the newborn resulting from the administration of analgesics to the mother during childbirth.

The MAH has been working with a variety of healthcare bodies involved in drug addiction treatment, including NHS Scotland, via the Scottish Drugs Forum and has been requested to make commercially available a presentation of Prenoxad 1mg/ml Injection that is suitable for use in a non-medical setting (i.e. in the community) by opioid misusers to reverse respiratory depression due to known or suspected opioid overdose by illicit opiate users and those in receipt of opiate substitution therapy.

This request is supported by a review conducted by the Advisory Council on the Misuse of Drugs (ACMD) published in May 2012, the purpose for which was to provide the UK Government with advice on whether naloxone should be made more widely available in order to prevent future drug-related deaths.

The ACMD wrote to the MHRA in 2009, stating that wider provision of naloxone to those likely to come into contact with, or caring for, drug misusers could provide benefits. The MHRA responded by stating it had no objections in principle to proposing changes to medicines legislations along these lines. The MHRA sought the views of the Department of Health to establish if they supported a change in the law, to allow persons who may be in contact with drug misusers to obtain supplies for use in an emergency, and to seek views on how such persons could be defined. The Department of Health stated that further consideration needed to be informed by the outcomes of the National Treatment Agency for Substance Misuse (NTA) overdose and naloxone programme for families and carers. The ACMD report considers the findings of the NTA naloxone programme.

Naloxone is a prescription-only medicine in the UK and, as it is a parenteral preparation, can only be administered by individuals with a prescription or appropriate medical practitioners. Some parenteral medicines can be given by injection by anyone for the purposes of saving a life e.g. adrenaline, atropine, glucagon, glucose, etc. In June 2005, the UK added naloxone to this list so that it too can be administered by anyone for the purpose of saving a life. It can be supplied to named individuals at risk of opioid overdose via a prescription or a Patient Group Direction (PGD) or Patient Specific Direction (PSD). However, it cannot currently be prescribed or supplied to a carer, peer or member of staff on behalf of a drug user and cannot be given to anyone without the drug user’s informed consent.
The NTA launched an overdose and naloxone training programme for family and carers of opiate users in 2009. The pilots ran at 16 sites in England from July 2009 to February 2010 and recruited 495 carers who were trained to respond to an overdose using basic life support. At 15 of the sites, carers were also trained to administer naloxone. There were 18 overdoses since the period of training where carers used naloxone and two where basic life support was used. All the drugs users survived the overdose. Pilot site staff, carers and service users found the training to be beneficial. All felt it made sense to train those people most likely to be present when users were taking drugs and running the risk of an overdose. This is often family members, but also other users.

A similar successful programme has been running nationally in Scotland since June 2011, although in local areas such as Glasgow the programme has been running longer. In March 2011, the Scottish Lord Advocate issued a guideline that approves authorised prescribers to supply naloxone to individuals likely to come into contact with those at risk of opiate overdose. Naloxone is now available in almost all Scottish Alcohol & Drug Partnerships (ADPs). The ‘naloxone kits’ are prepared in limited quantities as “Specials” by local modification of a licenced product that is identical to Prenoxad 1mg/ml Injection (Naloxone Hydrochloride Injection 1 mg/ml, licensed to Aurum Pharmaceuticals under PL 12064/0060).

The Welsh Government launched the Take Home Naloxone (THN) demonstration project in selected areas in September 2009. This was to test the feasibility of expanding the scheme nationwide. The evaluation recommended a national naloxone programme be rolled out.

The ACMD report concludes by making three recommendations to the UK Government:

1: Naloxone should be made more widely available, to tackle the high numbers of fatal opioid overdoses in the UK.

2: Government should ease the restrictions on who can be supplied with naloxone

3: Government should investigate how people supplied with naloxone can be suitably trained to administer it in an emergency and respond to overdoses

Discussion:
The existing available data supports the efficacy and use of the product in the indication. The change involves the way the product is made available. Recommendations of the ACMD are considered in relation to the application.

1: **Naloxone should be made more widely available, to tackle the high numbers of fatal opioid overdoses in the UK.**

Heroin (diamorphine) represents the predominant cause of drug-related death in the UK, with 1061 deaths attributed out of the 1930 drug related deaths reported in 2010 (Department of Health, 2011).

Most drug overdose deaths occur in the presence of others and there are data to show that, given appropriate instruction and education, these observers (often family members or other addicts) would be willing to intervene.

The pilot studies outlined above and discussed in more detail in the ACMD report suggest benefit in the scheme. It is known that most heroin related deaths occur within 1-3 hours from
the time of injection. In order to reduce the number of deaths due to overdose, it is, therefore, critical that the subject receives supportive care and naloxone at the earliest opportunity.

In the “take-home setting”, due to ease of administration, naloxone is administered by intramuscular (i.m.) injection, resulting in a slower onset of action than occurs with intravenous administration. Therefore, it is also necessary to apply CPR as part of the emergency treatment routine to bridge the time lag before i.m. naloxone achieves efficacious plasma levels.

From the data presented in the ACMD report, it is clear that, with sufficient training in both the administration of i.m. naloxone and CPR, naloxone intervention can be applied by drug users, their family members or carers and other users to treat acute opioid overdose. Experience obtained across the UK as well as in other countries shows that providing naloxone for emergency use in a community setting has resulted in lives saved and has the potential to impact on drug related deaths.

2: Government should ease the restrictions on who can be supplied with naloxone

The efficacy of naloxone as an opioid reversal agent is not questioned and when administered appropriately it will undoubtedly save lives. The key question is who to make it available to.

The proposed wording for Section 4.1 of the SmPC is as follows:

“Prenoxad Injection is intended for emergency use in the home or other non-medical setting by appropriate individuals or in a health facility setting for the complete or partial reversal of respiratory depression induced by natural and synthetic opioids, including methadone, diamorphine (diacetylmorphine (INN)) and certain other opioids such as dextropropoxyphene and certain mixed agonist/antagonist analgesics: nalbuphine and pentazocine.

For this reason Prenoxad Injection should be carried by persons at risk of such events.

It may also be used for the diagnosis of suspected acute opioid overdose.”

This wording is appropriate. To be of any impact, the naloxone must be available where and when required and it therefore seems most appropriate that, in addition to treatment centres, drug users carry the kit themselves.

Naloxone is a relatively safe drug and there are no reports of toxicity in overdose. The pre-filled syringe will obviously limit the amount that can be given in any episode to a dose well within the approved dose range.

However, there are potential indirect risks which require consideration:

- Potential for an increased risk of bystanders failing to call for an ambulance for fear of becoming involved with police services if an overdose can be treated in-situ.

- Risk of a naloxone treated individual refusing ambulance transport, particularly if they are experiencing opioid withdrawal symptoms.

- Potential for delayed respiratory depression given the shorter half-life of naloxone relative to that of heroin.
- The availability of naloxone in the community might also lead to more risky behaviour from addicts themselves. However, there is no evidence of this occurring from existing naloxone take home programmes that are in place.

A Risk Management Plan (RMP) is provided in support of this type II variation because this will be the first naloxone injection to be authorised in the UK for administration by non-healthcare professionals in the community and there is concern that this may lead to patients not seeking the medical attention they need.

Given that naloxone is a well known active substance, the proposed RMP focuses on the potential risks associated with this particular application i.e. use in the community setting by non-healthcare professionals.

**ASSESSMENT OF THE RMP**

**2.1 SAFETY SPECIFICATION**

**2.1.1 Non-Clinical Safety**

The non-clinical information is based on medical literature and includes limited information on exposure to naloxone in animal reproductive (no embryotoxic or teratogenic effects in mice and rats at 4-times and 8-times the adult human dose) and developmental studies (increased neonatal death). The SmPC states that naloxone should only be used with caution in pregnancy.

Overall, the MAH considers that there are no safety concerns arising from non-clinical data and no requirements for additional studies.

**2.1.2 Clinical Safety**

No clinical studies have been performed with Prenoxad 1mg/ml Injection as this is a generic version of a well-established drug substance. The clinical safety of naloxone is well established and the MAH refers to medical literature to describe the safety profile of the drug substance following use for reversal of post-operative opioid analgesia and reversal of respiratory depression following acute opioid overdose. The MAH considers that no further clinical studies are required. Data available from published naloxone programmes demonstrate the clinical safety and effectiveness of naloxone for the proposed use in the community.

**Epidemiological study exposure**

The MAH has included in this section of the RMP information about the use of the unlicensed “Special” product in harm reduction programmes in Scotland (using a product identical to Prenoxad 1mg/ml Injection) and similar programmes using other naloxone products across the UK.

**Limitations of the Human Safety Database**

The MAH has not performed any clinical studies and refers to the medical literature and extensive approved clinical use of naloxone in general, including in different indications and patient populations including the anticipated patient population in the community setting. This includes use for the reversal of respiratory depression caused by illicit use of opioids and use of opioids in surgery; and reversal of respiratory depression in neonates following the use of pethidine during labour or secondary to illicit use of opioids by the mother during pregnancy.
The MAH considers that the existing experience of use of naloxone in a wide range of clinical indications and patient populations is sufficient. This variation does not seek an indication for administration by non-healthcare professionals to children in the community.

**Projected post-authorisation usage**
The MAH has based its projections for post-authorisation usage on the size of the target population (105,000 opiate injectors in the UK based on statistics provided in the 2012 Advisory Council on the Misuse of Drugs Guidance Note on naloxone) and the potential uptake by health services to fund and provide “take-home” naloxone in the community. However, the estimated number is based on the number of kits issued rather than kits used.

**Adverse events/adverse reactions**
As discussed previously, the side effect profile of naloxone is well-established following extensive clinical use and the MAH refers to the SmPCs of approved products (including the reference product) and the medical literature in support of this.

**Identified risks**
The MAH has included five important identified risks of naloxone in this section of the RMP. These are:

1) Precipitation of acute opioid withdrawal effects
2) Cardiovascular adverse effects (including serious arrhythmias and hyper- and hypotension)
3) Hypersensitivity
4) Delayed respiratory depression due to short half-life of naloxone
5) Lack of effect in mixed overdose (concomitant overdose of non-opioid drugs) or inappropriate use of naloxone (where opioid overdose is not involved)

**Potential risks**
In this section of the RMP, the MAH has included indirect potential risks, not product related, that may be associated with the use of naloxone in the non-medical setting (i.e. in the context in which Prenoxad 1mg/ml Injection is intended to be used). These are:

1) Failure to seek medical attention/Refusal of ambulance transport
2) Rebound opioid use after recovery
3) Encouraging risky behaviour
4) Use by non-medical/non-healthcare professionals
5) Failure to perform CPR
6) Needle/syringe diversion
7) Needle-stick injury to person administering injection
8) Failure to dispose of needles safely (needlestick injury and transmission of infectious disease risk to public if used and discarded outside of home)

**Pharmacological class effects**
The known effects of opioid antagonists have been suitably described.

**Potential for transmission of infectious agents**
The MAH discusses the possibility of needle sharing in this patient population and the associated risk of transmission of HIV or other infections but considers that the provision of two sterile needles and education of the target population will mitigate this risk. The risks of injection equipment sharing and blood borne virus transmission are risks that drug and needle exchange services are familiar with and deal with routinely. The possibility of needle stick
injury to the person administering the injection and subsequent risk of infection as well as the consequences of discarding used needles in public places are also considered.

**Potential for misuse for illegal purposes**
The risk of use of the needle/syringe for illegal purposes is considered.

**Summary of ongoing safety concerns**
The identified and potential risks associated with administration of Prenoxad 1mg/ml Injection by people who are not healthcare professionals are suitably summarised.

**2.2 PHARMACOVIGILANCE PLAN**
Although naloxone is a generic medicine and under the new Pharmacovigilance legislation PSURs are not required for generic products, the MAH has committed to provide annual PSURs for the first 3 years of marketing, given the novel use of the product in a non-medical setting.

There is a concern that if the product is administered to the addict by a non-healthcare professional in the community this could mean that patients will not seek the medical treatment that they may still need following administration of naloxone and that the availability of the ‘antidote’ may encourage more risky behaviour. These risks may not be captured via routine pharmacovigilance practices as they do not represent direct adverse events arising from the administration of Prenoxad 1mg/ml Injection to patients. Therefore, the MAH has committed to obtain information to help evaluate these indirect risks.

The MAH’s approach will be to work within the drug treatment frameworks with accredited providers of drug treatment services as discussed in the RMP. The MAH will seek to acquire information from various accredited sources utilising databases already in place under the auspices of the services responsible for providing naloxone within an overall harm reduction strategy.

**2.3 EVALUATION OF THE NEED FOR RISK MINIMISATION ACTIVITIES**
Routine risk minimisation activities such as the provision of suitable product information, labelling and packaging are in place to mitigate the identified and potential risks associated with the use of Prenoxad 1mg/ml Injection Community Pack. However, the MAH will also provide suitable educational/training materials for the product. According to the RMP guideline, these are considered to be additional risk minimisation activities.

**Potential for medication errors**
The potential for inadvertent administration of the complete contents of the syringe in one administration rather than in several 0.4mL doses every 2-3mins and the possible consequences of this are discussed adequately.

**2.4 RISK MINIMISATION PLAN**
Given that it is intended that Prenoxad 1mg/ml Injection Community Pack will be administered by non-healthcare professionals, the patient information leaflet and training and educational materials for both the patient and the person nominated by the patient to administer the injection in an emergency are key. Suitable details of these are provided and the MAH has committed to review these materials within 6 months of first marketing the product and then annually for 3 years.

**2.5 SUMMARY OF RISK MANAGEMENT PLAN**
This is a suitable summary of the RMP.
CONCLUSIONS
The pharmacological and safety profiles of naloxone are well established. This RMP has been submitted at the request of the MHRA because of concerns about the change of use for this product and the potential direct and indirect risks associated with its use.

The proposed Risk Management Plan for Prenoxad 1mg/ml Injection captures all identified and potential risks and is satisfactory.

3: Government should investigate how people supplied with naloxone can be suitably trained to administer it in an emergency and respond to overdoses

Section 4.2 of the SmPC details both the dosage of naloxone to be administered and broad details on how to perform basic life support:

“Prenoxad Injection may only be made available once the prescriber has assessed the suitability and competence of a client or representative to administer naloxone in the appropriate circumstances.

Prenoxad Injection is for administration by intramuscular injection.

Prenoxad Injection is administered as a part of a resuscitation intervention in suspected overdose casualties, where opioid drugs may be involved or suspected. It may need to be used in a non-medical setting. Therefore, the prescriber should take appropriate steps to ensure that the patient thoroughly understands the indications and use of Prenoxad Injection. The prescriber should review with the patient or any other person who might be in a position to administer Prenoxad Injection to a patient experiencing a suspected opioid overdose event.

In patients where breathing does not appear to be normal
In patients where breathing does not appear to be normal administration of Prenoxad Injection should be preceded by calling emergency services and requesting an ambulance. Following this, 30 chest compressions and if possible 2 rescue breaths (Basic Life Support SINGLE CYCLE) should be given; 0.4ml Prenoxad Injection solution should then be administered by intramuscular injection into the outer thigh muscle or muscles of the upper arm, through clothing if necessary. A further 3 cycles of chest compressions and rescue breaths should then be given followed by administration of 0.4ml Prenoxad Injection. Three cycles of chest compression and rescue breaths should take approximately 2 minutes. This should be repeated until an ambulance arrives or the patient begins breathing normally / regains consciousness. The patient when breathing normally or has regained consciousness should be placed in the recovery position (lying on their side, mouth open pointing towards the ground) and observed continuously.

In patients were breathing is normal but the patient is unrousable or suspected to be unconscious.
Patient should be placed in the recovery position (lying on their side, mouth open pointing towards the ground). 0.4ml Prenoxad Injection solution should be administered by intramuscular injection into the outer thigh muscle or muscles of the upper arm, through clothing if necessary, and an ambulance should be called, 0.4ml Prenoxad Injection solution should then be administered every 2-3 minutes and continued until the ambulance arrives and or the patient regains consciousness. The patient should be continuously observed but particularly their breathing. If there is a decrease in breathing it is important that 0.4ml Prenoxad Injection solution is given every 2-3 minutes.
Parenteral drug products should be inspected visually for particulate matter and
discolouration prior to administration whenever solution and container permit.

**Adults:**

**Opioid overdosage (known or suspected)**

**Use by individuals in the community**
400 micrograms or 0.4ml of Prenoxad Injection solution by intramuscular injection into the
outer thigh or muscles of the upper arm as part of the resuscitation intervention. The dose of
0.4ml can be repeated every 2-3 minutes in subsequent resuscitation cycles until the contents
of a syringe are used up.

N.B. The duration of action of certain opioids can outlast that of an IV bolus of Naloxone,
e.g. dextropropoxyphene, dihydrocodeine and methadone. In situations where one of these
opioids is known or suspected it is recommended that an infusion of Naloxone be used to
produce sustained antagonism to the opioid without repeated injection.

**Children**
The Prenoxad Injection presentation is not intended to be used for children in the home
setting other than by an appropriately trained healthcare professional. In the event of a child
being given or taking an opioid inappropriately an ambulance should be called and
resuscitation started if required.

**Neonatal Use**
Naloxone should only be used in Neonates under medical supervision.

**Elderly**
Use as for adults.”

Two elements of training are necessary: training appropriate physicians, nurses, pharmacists
etc in the competencies necessary to be designated within a drug treatment service and who
will provide the training of clients (the name given to drug service users) and representatives,
assess suitability and competence to administer naloxone in the appropriate circumstances as
well as prescribing and documenting the naloxone supply and; delivering training to the
service clients and representatives.

Both elements are the responsibility of the drug treatment services, structures and systems for
naloxone are already undertaken by these services in many localities and in any event the
approach is common to other parts of drug treatment services.

In Scotland and Wales there are approved National Training Manuals for use during training
programmes for take home naloxone (THN). There is not yet an overarching THN guidance
document for England or for Northern Ireland; in particular service development in Northern
Ireland has lagged behind that in the other UK regions.

The Welsh Assembly Government’s 2010 Guidance and Training Protocol summarises the
targeted outcome of training for programme participants that they should be able to:

- Identify the key risks for accidental overdose
- Recognise the signs and symptoms of a drug overdose
- Keep themselves safe, e.g. look out for used needles if dealing with someone who has overdosed
- Assess vital life signs and to provide first aid
- Place someone in the recovery position
- Give mouth to mouth resuscitation
- Outline common myths and dangerous practices in overdose response
- Discuss what has been covered in the training session

Participants should have gained in-depth knowledge of naloxone and its effects and also practiced injecting naloxone (intramuscular injection, often practicing injection into an orange). Each individual must have signed a consent form. An information sheet should also be distributed.

It should be noted that the various drug services already provide training and counseling to clients of the THN service where these programmes already exist. For example, many needle exchange clinics already counsel clients and provide hepatitis B vaccination under patient group direction arrangements and are comfortable with the process. Opiate substitution services also provide a range of counseling and other support to increase the client’s chances of rehabilitation. Such clinics and services are therefore best placed to deliver THN services including the necessary training. The drug services must retain ownership and responsibility for this as they are also subject to audit, are accountable for performance and provide data for national statistics on drug misuse and harm prevention interventions.

There is a wealth of training materials for THN services available in the public domain as well as the validated materials developed by the Scottish and Welsh harm reduction services on which individual NHS trusts can base their individual programmes. These include PowerPoint slide presentations, training videos, leaflets and pamphlets as well as assessment questionnaires.
Examples of PGD protocols and training materials are available for reference at independent sites including Naloxone.org.uk, Overdose prevention Alliance, Harm Reduction Coalition and Harm Reduction International.

The MAH asserts that it is not the role of the MAH of any individual naloxone product that may be used for THN to provide training to either the drug services or to the individual programme participants. Nor is the MAH of any one naloxone product in a position to monitor the success or otherwise of THN as a harm reduction intervention. Firstly, THN represents only one harm reduction approach to opioid overdose along with opioid substitution, needle exchange, social support and education. It will not be possible to attribute any change in the statistics of drug-related deaths to THN or to any other intervention. Even in the case of an individual overdose, the survival or death of the patient may be due to other factors including the time delay since drug injection, the presence of multiple drugs and/or alcohol, the effectiveness of life support techniques applied at the scene, the willingness of bystanders to take appropriate action and the speed with which follow up medical attention is received. There are many generic naloxone products approved and marketed in the UK and it is likely that ultimately multiple products will achieve approval for THN supply. However, the MAH for Prenoxad 1mg/ml Injection commits to provide a platform of educational tools on the safe and effective use of Prenoxad 1mg/ml Injection in this patient population.

The Prenoxad educational materials will be available on a specific website. The site will be tailored for physicians, pharmacists and patients. Contents will include a Prescribers Guide, a Pharmacist Guide and Patient Information. In addition the site will contain the Patient Information Leaflet and Summary of Product Characteristics. To further help ensure safe and
appropriate use of the Prenoxad 1mg/ml Injection the site will contain video footage and picture guides on assembly and use of the Community Pack. It is further proposed that the site will contain information on the role of naloxone in harm reduction programmes and opioid overdose minimisation programmes.

Materials on the website will be made available for third parties who host resources for drug service teams and associated specialists working and delivering harm reduction programmes.

Prenoxad 1mg/ml Injection website will also be featured on the Martindale Pharma website.

**Educational material via social media**
The MAH will also provide material on Prenoxad 1mg/ml Injection to organisations providing content in harm reduction via social media and “Apps” for smartphones.

**Product training**
Materials will be prepared on Prenoxad 1mg/ml Injection for formal product training by drug services delivering and implementing harm reduction programmes which will involve prescribing of the Prenoxad 1mg/ml Injection.

The MAH will ensure all staff involved in the marketing of the Prenoxad 1mg/ml Injection are fully trained on the product and undergo additional training on harm reduction programmes and opiate overdose.

**Monitoring use of Prenoxad 1mg/ml Injection**
The MAH will create an advisory board to review the roll out and uptake of the Prenoxad 1mg/ml Injection. The advisory board shall meet at least twice a year with a first meeting no later than 6 months post first commercial sale and shall review the MAH’s marketing activities and provide strategic guidance and recommendations to ensure safe and appropriate use of the Prenoxad 1mg/ml Injection. Attendees for the advisory board will include physicians with specific expertise in the area of THN as well as drug treatment service providers and allied healthcare professionals.

The MAH will conduct regular surveys, at least once per year, the first survey is to be no later than 6 months post first commercial sale, with drug service teams to review uptake and usage of the Prenoxad 1mg/ml Injection in order to ensure that all support material is up to date and to gain an understanding of the framework and programmes in which the product is being prescribed.

Recognising the inherent complexity in linking the use of Prenoxad 1mg/ml Injection with a reduction in opiate overdose or drug related death, the MAH is committed to supporting drug service treatment providers in terms of the outputs from programmes using Prenoxad 1mg/ml Injection. The MAH plans to acquire under license via a third party anonymised data from the NHS which will illustrate the number and costs of hospital consultations and admissions by episode or patient from opiate overdose. Such data can be supplied tailored to a defined geography.

It is understood how staff in a treatment facility might be trained to recognise an opioid overdose, administer basic life support and administer i.m. naloxone. It is less obvious how this might apply to family or carers of an i.v. drug user, or other drug users themselves. The MAH lays this responsibility with the prescriber, while ensuring that suitable training materials are readily available.
This is appropriate and such training is already practised by those specialist treatment centres providing THN as part of a patient group directive.

**Conclusion**
The proposed variation is clinically acceptable.
SUMMARY OF PRODUCT CHARACTERISTICS

Following approval of the variation on 11 December 2012 the SmPC was updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

Following approval of the variation on 11 December 2012 the Patient Information Leaflet was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflets for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING

Following approval of the variation on 11 December 2012 the following updated product labelling has been incorporated into the Marketing Authorisation:
UKPAR Naloxone Hydrochloride 1 mg/ml Injection

For intramuscular injection.
Keep out of the sight and reach of children. Store in the original container.
Do not store above 25°C. Single patient use only.
Any unused injection solution should be discarded
Do not use if seal or packaging is damaged.

Aurum Pharmaceuticals Ltd.
Bampton Rd. Romford RM3 8UG. UK

Contains: 1 x 2ml Prefilled Syringe and 2 Needles

Prenoxad™ Injection
Naloxone Hydrochloride 1mg/ml solution for injection

OBTAIN MEDICAL ASSISTANCE AS SOON AS POSSIBLE.
Inject 0.4ml (400 micrograms) into the outer thigh muscle or upper arm muscle.
If no response repeat at 2-3 minute intervals.