Part VI: Summary of the risk management plan – Prenoxad France

Summary of risk management plan for Prenoxad® (naloxone hydrochloride) - France

This is a summary of the risk management plan (RMP) for Prenoxad. The RMP details important risks of Prenoxad, how these risks can be minimised.

Prenoxad's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Prenoxad should be used.

I. The medicine and what it is used for

Prenoxad is to be used in individuals at risk of opioid overdose. The product is intended to be used in the community by opioid users, those who may witness overdoses, including other drug users, families and carers.

Deaths due to overdose of heroin and other opioid drugs from misuse or abuse represent a significant public health worldwide. It is known that almost a quarter of the adult population of Europe have used illicit drugs during their lifetime. Overall, there was a higher prevalence in the 15-34-year olds compared to older groups. In France, in 2014, use of heroin at least once in life in the general population is 1.5% in the 18-64-year-olds while it is 42 % for cannabis, 5.6% for cocaine, 4.3% for ecstasy, 2.3% for amphetamine. Poly drug use was reported in 32.7% and concomitant alcohol abuse in 83.1%.

Prenoxad contains the medicine naloxone. Naloxone belongs to a group of medicines that reverse the action of opioid drugs e.g. diamorphine (heroin), methadone, nalbuphine, pentazocine.

Prenoxad is used to:

reverse the action of opioid drugs e.g. if people have been given or taken an overdose of these drugs if people are at risk of an opioid overdose, or liable to witness one, they should always carry their Prenoxad with them. It is designed as an emergency rescue treatment, but they should still get medical attention as soon as possible.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Prenoxad, together with measures to minimise such risks and the proposed studies for learning more about Prenoxad's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Prenoxad, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Prenoxad is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Summary of safety concerns	
Important identified risks	• reoccurrence of respiratory depression • precipitation of opioid withdrawal syndrome • lack of effect with mixed overdose or inappropriate use in non-opioid overdose • cardiovascular effects
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk: Reoccurrence of respiratory depression	
Evidence for linking the risk to the medicine	Naloxone is a short acting opioid antagonist and subsequent doses may be needed if normal breathing is not restored or diminishes. Naloxone administered intramuscularly acts during around one to two hours while average opioid overdose duration is from two hours to four hours in case of intravenous administration, from six hours in case of oral administration of immediate release opioids or subcutaneous administration, from 10 to 12 hours in case of oral use of extended release opioid and from 36 to 48 hours in case of methadone. The half-life of naloxone is shorter than that of heroin and respiratory depression has been shown to occur in 15% of suspected overdose patients treated with naloxone (Sporer et al, 2007). This risk is minimised by appropriate training and the possibility to administer up to 5 doses of 0.4 mL naloxone from the prefilled syringe, thus increasing the likelihood of survival. Administration of 5 doses at these intervals will take approximately 15 minutes, a time window close to the response times of most emergency services. The training emphasises the need to continue with life support/CPR until

	the emergency services arrive should all of the naloxone have been administered and the patient is still not conscious/breathing properly.
Risk factors and risk groups	Opioid dependent individuals, especially after long acting opioids (e.g. heroin, methadone). Return of respiratory depression after initial dose of naloxone wears off.
Risk minimisation measures	**Routine risk minimisation measures** Information, guidance and warnings are contained in the SmPC and PIL of Prenoxad The pack size of the products including one pre-filled syringe. **Additional risk minimisation measures** Additional risk minimisation activities based on the provision of training by the person who provides naloxone and making available appropriate educational materials (Dispensing Professional Guide, Patient Guide, videos and Patient Card) are proposed by the MAH/Applicant.
Important identified risk: Precipitation of opioid withdrawal syndrome	
Evidence for linking the risk to the medicine	Opioid withdrawal symptoms may be precipitated in subjects physically dependent on opioids by administration of opioid antagonists, including naloxone. Symptoms may appear within 2 minutes of naloxone administration and subside within 2 hours.
Risk factors and risk groups	Opioid dependent individuals Unpleasant symptoms may lead opioid dependent individual to seek further opioid dose
Risk minimisation measures	**Additional risk minimisation measures** Additional risk minimisation activities based on the provision of training by the person who provides naloxone and making available appropriate educational materials (Dispensing Professional Guide, Patient Guide, videos and Patient Card) are proposed by the MAH/Applicant
Important identified risk: Lack of effect with mixed overdose or inappropriate use in non-opioid overdose	
Evidence for linking the risk to the medicine	Naloxone is effective for the reversal of opioid agonist overdose but is not completely effective in the reversal of overdose due to non-opioids or mixed agonists/antagonists such as buprenorphine (Martindale On-Line, 2012); or in the event of poly-drug use (Brand, 2006). Naloxone will reverse the overdose effects that are due to the opioid component of a poly-drug cocktail but not of non-opioid effects.

Risk factors and risk groups	Poly-drug abusers; abusers of drugs other than opioids Abuse drugs with mechanisms of action other than opioids
Risk minimisation measures	**Routine risk minimisation measures** Information, guidance and warnings are contained in the SmPC and PIL of Prenoxad The pack size of the products including one pre-filled syringe. **Additional risk minimisation measures** Additional risk minimisation activities based on the provision of training by the person who provides naloxone and making available appropriate educational materials (Dispensing Professional Guide, Patient Guide, videos and Patient Card) are proposed by the MAH/Applicant.
Important identified risk: Cardiovascular events	
Evidence for linking the risk to the medicine	At very high dose, serious cardiovascular events including hypertension, arrhythmia, pulmonary oedema and cardiac arrest have been reported in post-operative patients treated with opioid analgesics.
Risk factors and risk groups	Post-operative patients treated with opioid analgesics. Opioid dependent subjects Medical history of cardiovascular disorders Concomitant use of drugs with cardiovascular effects
Risk minimisation measures	**Routine risk minimisation measures** Information, guidance and warnings are contained in the SmPC and PIL of Prenoxad The pack size of the products including one pre-filled syringe. **Additional risk minimisation measures** Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation, or specific obligation of Prenoxad.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Prenoxad.

Part VI: Summary of the risk management plan - Prenoxad UK and DCP

Summary of risk management plan for Prenoxad® (naloxone hydrochloride) – UK and DCP

This is a summary of the risk management plan (RMP) for Prenoxad. The RMP details important risks of Prenoxad, how these risks can be minimised.

Prenoxad's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Prenoxad should be used.

I. The medicine and what it is used for

Prenoxad is to be used in individuals at risk of opioid overdose. The product is intended to be used in the community by opioid users, those who may witness overdoses, including other drug users, families and carers.

Deaths due to overdose of heroin and other opioid drugs from misuse or abuse represent a significant public health worldwide. It is known that almost a quarter of the adult population of Europe have used illicit drugs during their lifetime. Overall, there was a higher prevalence in the 15-34-year olds compared to older groups. In France, in 2014, use of heroin at least once in life in the general population is 1.5% in the 18-64-year-olds while it is 42 % for cannabis, 5.6% for cocaine, 4.3% for ecstasy, 2.3% for amphetamine. Poly drug use was reported in 32.7% and concomitant alcohol abuse in 83.1%.

Prenoxad contains the medicine Naloxone. Naloxone belongs to a group of medicines that reverse the action of opioid drugs e.g. diamorphine (heroin), methadone, nalbuphine, pentazocine.

Prenoxad is use:

- to reverse the action of opioid drugs e.g. if people have been given or taken an overdose of these drugs
- if people are at risk of an opioid overdose, or liable to witness one, they should always carry their Prenoxad with them. It is designed as an emergency rescue treatment, but they should still get medical attention as soon as possible.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Prenoxad, together with measures to minimise such risks and the proposed studies for learning more about Prenoxad's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Prenoxad, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Prenoxad is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Summary of safety concerns	
Important identified risks	• reoccurrence of respiratory depression • precipitation of opioid withdrawal syndrome • cardiovascular effects • lack of effect with mixed overdose or inappropriate use in non-opioid overdose
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk: Reoccurrence of respiratory depression	
Evidence for linking the risk to the medicine	Naloxone is a short acting opioid antagonist and subsequent doses may be needed if normal breathing is not restored or diminishes. Naloxone administered intramuscularly acts during around one to two hours while average opioid overdose duration is from two hours to four hours in case of intravenous administration, from six hours in case of oral administration of immediate release opioids or subcutaneous administration, from 10 to 12 hours in case of oral use of extended release opioid and from 36 to 48 hours in case of methadone. The half-life of naloxone is shorter than that of heroin and respiratory depression has been shown to occur in 15% of suspected overdose patients treated with naloxone (Sporer et al, 2007). This risk is minimised by appropriate training and the possibility to administer up to 5 doses of 0.4 mL naloxone from the prefilled syringe, thus increasing the likelihood of survival. Administration of 5 doses at these intervals will take approximately 15 minutes, a time window close to the response times of most emergency services. The training emphasises the need to continue with life support/CPR until the emergency services arrive

	should all of the naloxone have been administered and the patient is still not conscious/breathing properly.
Risk factors and risk groups	Opioid dependent individuals, especially after long acting opioids (e.g. heroin, methadone). Return of respiratory depression after initial dose of naloxone wears off.
Risk minimisation measures	**Routine risk minimisation measures** Information, guidance and warnings are contained in the SmPC and PIL of Prenoxad The pack size of the products including one pre-filled syringe. **Additional risk minimisation measures** Additional risk minimisation activities based on the provision of training by the person who provides naloxone and making available appropriate educational materials (Issuers Guide, Client Guide, videos are proposed by the MAH).
Important identified risk: Precipitation of opioid withdrawal syndrome	
Evidence for linking the risk to the medicine	Opioid withdrawal symptoms may be precipitated in subjects physically dependent on opioids by administration of opioid antagonists, including Naloxone. Symptoms may appear within 2 minutes of naloxone administration and subside within 2 hours.
Risk factors and risk groups	Opioid dependent individuals Unpleasant symptoms may lead opioid dependent individual to seek further opioid dose
Risk minimisation measures	**Additional risk minimisation measures** Additional risk minimisation activities based on the provision of training by the person who provides naloxone and making available appropriate educational materials (Issuers Guide, Client Guide, videos are proposed by the MAH).
Important identified risk: Lack of effect with mixed overdose or inappropriate use in non-opioid overdose	
Evidence for linking the risk to the medicine	Naloxone is effective for the reversal of opioid agonist overdose, but is not completely effective in the reversal of overdose due to non-opioids or mixed agonists/antagonists such as buprenorphine (Martindale On-Line, 2012); or in the event of poly-drug use (Brand, 2006). Naloxone will reverse the overdose effects that are due to the opioid component of a poly-drug cocktail but not of non-opioid effects.
Risk factors and risk groups	Poly-drug abusers; abusers of drugs other than opioids Abuse drugs with mechanisms of action other than opioids
Risk minimisation measures	**Routine risk minimisation measures**

	Information, guidance and warnings are contained in the SmPC and PIL of Prenoxad The pack size of the products including one pre-filled syringe. **Additional risk minimisation measures** Additional risk minimisation activities based on the provision of training by the person who provides naloxone and making available appropriate educational materials (Issuers Guide, Client Guide, videos are proposed by the MAH).
Important identified risk: Cardiovascular events	
Evidence for linking the risk to the medicine	At very high dose, serious cardiovascular events including hypertension, arrhythmia, pulmonary oedema and cardiac arrest have been reported in post-operative patients treated with opioid analgesics.
Risk factors and risk groups	Post-operative patients treated with opioid analgesics. Opioid dependent subjects Medical history of cardiovascular disorders Concomitant use of drugs with cardiovascular effects
Risk minimisation measures	**Routine risk minimisation measures** Information, guidance and warnings are contained in the SmPC and PIL of Prenoxad The pack size of the products including one pre-filled syringe. **Additional risk minimisation measures** Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation, or specific obligation of Prenoxad.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Prenoxad.