

## **Public Assessment Report**

**Lidocaine 1% w/v Solution for Injection (PL 20910/0011)  
Lidocaine 2% w/v Solution for Injection (PL 20910/0012)**

**Taro Pharmaceuticals (Ireland) Limited**

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## LAY SUMMARY

The MHRA today granted Taro Pharmaceuticals (Ireland) Limited Marketing Authorisations (licences) for the medicinal products Lidocaine 1% w/v Solution for Injection (PL 20910/0011) and Lidocaine 2% w/v Solution for Injection (PL 20910/0012). These are prescription only medicines (POM) for use as a local anaesthetic, i.e. to numb specific parts of the body and prevent pain during medical procedures or surgery.

Lidocaine 1% and 2% w/v Solution for Injection contain the active ingredient lidocaine hydrochloride, which belongs to a group of medicines called amide-type local anaesthetics. These produce a loss of feeling or sensation that is confined to one part of the body.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Lidocaine 1% and 2% w/v Solution for Injection outweigh the risks, hence Marketing Authorisations have been granted.

**Lidocaine 1% w/v Solution for Injection (PL 20910/0011)**  
**Lidocaine 2% w/v Solution for Injection (PL 20910/0012)**

**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Lidocaine 1% w/v Solution for Injection (PL 20910/0011) and Lidocaine 2% w/v Solution for Injection (PL 20910/0012) on 15<sup>th</sup> August 2007. The products are prescription-only medicines.

These are abridged applications for two strengths of Lidocaine Solution for Injection, submitted according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products Lignocaine Injection BP 1% and 2% w/v Solution for Injection (Antigen Pharmaceuticals Limited, Ireland).

The products contain the active ingredient lidocaine hydrochloride, an amide-type local anaesthetic indicated for use in infiltration anaesthesia, intravenous regional anaesthesia and nerve blocks.

## PHARMACEUTICAL ASSESSMENT

### DRUG SUBSTANCE

#### General Information

INN: Lidocaine hydrochloride BP (*Ph Eur monograph 0227*)

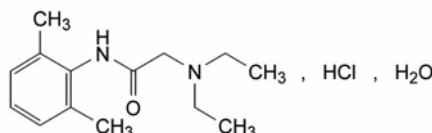
Molecular formula:  $C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$

Molecular weight: 288.8

Chemical names: 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide

ATC code: N01BB02

Structure:



General properties: A white, crystalline powder, very soluble in water, freely soluble in alcohol. It should be protected from light.

All aspects of drug substance manufacture are covered by an EDQM certificate of suitability.

The drug substance specification is satisfactory, the analytical methods used are appropriate and have been appropriately validated. Suitable batch analysis data have been provided showing compliance with the specification. All impurities have been adequately characterised and details of all reference standards used have been provided.

The drug substance is packaged in a transparent polyethylene bag, which is covered by an outer grey polyethylene bag and both bags tied with a polyamide cable tie. This bag is then placed in a drum with a metal closure. Satisfactory specifications have been provided for all packaging materials used. It has been confirmed that the polyethylene bags used are all in compliance with regulations concerning materials in contact with food.

Stability studies on the active substance have been performed according to current ICH guidelines. The data provided support a retest period of 5 years.

### DRUG PRODUCT

#### Other ingredients

Other ingredients consist of the pharmaceutical excipients, namely sodium chloride, hydrochloric acid 10% w/v, sodium hydroxide 10% w/v and water for injections. All excipients are controlled to the relevant Ph Eur monograph. Satisfactory certificates of analysis have been provided for all excipients showing compliance to their respective monographs.

The excipients are well-known and widely used in the pharmaceutical industry. None of the excipients used are of human or animal origin.

As pharmacopoeial methods are used, validation data is not required, and as the product is terminally sterilised, no evidence of the microbial quality of the excipients is required.

**Pharmaceutical development**

Satisfactory pharmaceutical development data have been provided

**Manufacture**

A description and flow-chart of the manufacturing method has been provided. Satisfactory batch formulae have been provided for both strengths of finished product.

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 each strength of product. The results appear satisfactory.

**Finished product specification**

The finished product specification is satisfactory.

There is currently a BP and USP monograph for the finished product. Most tests used in the finished product specification comply with the monograph. Where these tests do not comply, a full methodology of the analytical procedure has been provided, along with suitable validation data for the procedure.

Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used. Given the pharmacopoeial nature of the active and the simple method of manufacture, no additional impurities are expected and so no characterisation data for impurities has been provided.

**Container-closure system**

The finished product is stored in polypropylene ampoules of either 5ml or 10ml volume for the 1% strength and 5ml volume for the 2% strength. These are packed into an outer cardboard box, with 20 ampoules per box. Specifications and certificates of analysis have been provided for all packaging used. These are satisfactory. Compliance with the Ph Eur monograph for polypropylene use in containers/closures of parenteral and ophthalmic preparations has been shown.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set for both strengths, with the storage conditions "Do not store above 25°C". The product is to be used as soon as it is opened and any remaining product is to be discarded after first use.

**Bioequivalence**

As these are parenteral products that are administered by intravenous or intramuscular injection, no bioequivalence data are necessary. Essential similarity has been shown by a qualitative and quantitative content of the active substance for both the test and reference products.

**ADMINISTRATIVE****Expert Report**

A pharmaceutical expert report has been written by a suitably qualified person. It is a non-critical summary of the data and is satisfactory.

**Summary of Product Characteristics**

These are consistent with those for the reference products and are satisfactory.

**Labelling**

These are satisfactory.

**Patient Information Leaflet**

This is consistent with that for the reference products and is satisfactory.

**MAA Forms**

These are satisfactory.

**Conclusion**

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the test and reference products have been met with respect to qualitative and quantitative content of the active substance.

## **PRECLINICAL ASSESSMENT**

These applications for generic products claims essential similarity to Lignocaine Injection BP 1% and 2% w/v Solution for Injection (Antigen Pharmaceuticals Limited, Ireland), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.



## CLINICAL ASSESSMENT

### 1. INDICATIONS

Lidocaine is a local anaesthetic of the amide group. Lidocaine solution for injection is indicated for use in infiltration anaesthesia, intravenous regional anaesthesia and nerve blocks.

*These are consistent with the indications for the reference product.*

### 2. DOSE & DOSE SCHEDULE

The method of administration of lidocaine varies according to the procedure (infiltration anaesthesia, intravenous regional anaesthesia or nerve block).

The dosage should be adjusted according to the response of the patient and the site of administration. The lowest concentration and smallest dose producing the required effect should be given. The dosage varies depending on the area to be anaesthetised, vascularity of the tissues, number of neuronal segments to be blocked, individual tolerance and the anaesthetic technique. The lowest dosage needed to provide anaesthesia should be administered.

Unnecessarily high doses of local anaesthetics are to be avoided. In general, surgical anaesthesia (e.g. epidural administration) requires the use of higher concentrations and doses. When blocking smaller nerves, or when a less intense block is required, the use of a lower concentration is indicated. The volume of drug used will affect the extent and spread of anaesthesia. The maximum dose for healthy adults should not exceed 200 mg.

Care should be taken to prevent acute toxic reactions by avoiding intravascular injection. Careful aspiration before and during the injection is recommended. When a large dose is to be injected, e.g. in epidural block, a test dose of 3 – 5 ml of lidocaine containing adrenaline (epinephrine) is recommended. An accidental intravascular injection may be recognised by a temporary increase in heart rate. The main dose should be injected slowly while keeping in constant verbal contact with the patient. If toxic symptoms occur, the injection should be stopped immediately.

Children: The dosage should be calculated on a weight basis and should not exceed 5 mg/kg.

Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

*These are consistent with the dose and dosage schedule for the reference product.*

### 3. TOXICOLOGY

No formal data is provided under this heading and none are required for this application.

There is a non-clinical overview written by an appropriately qualified consultant. It is a satisfactory review of the non-clinical information provided.

- 4. CLINICAL PHARMACOLOGY**  
This application does not require the inclusion of a bioequivalence study as it is an application claiming essential similarity for a parenteral drug containing the same active substance in the same concentration as the reference product.
- 5. EFFICACY**  
No new data are submitted and none are required for this type of application.
- 6. SAFETY**  
No formal safety data are presented. The adverse events that can be expected are listed in the SPC and are consistent with those for the reference product.
- 7. CLINICAL OVERVIEW**  
There is a clinical overview written by a consultant to the pharmaceutical industry. It is a satisfactory review of the clinical information provided.
- 8. SUMMARY OF PRODUCT CHARACTERISTICS**  
This is consistent with the summary of product characteristics for the reference product.
- 9. PATIENT INFORMATION LEAFLET**  
This is satisfactory and consistent with that for the reference product.
- 10. LABELLING**  
This is satisfactory.
- 11. DISCUSSION**  
The data presented has shown that Lidocaine 1% and 2% Solution for Injection is essentially similar to Lignocaine Injection BP 1% and 2% w/v Solution for Injection.
- 12. RECOMMENDATIONS**  
The efficacy and safety of the products are satisfactory for the grant of product licences.

**OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT****QUALITY**

The important quality characteristics of Lidocaine 1% and 2% 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 benefit/risk balance.

**PRECLINICAL**

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

**EFFICACY**

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for Lignocaine Injection BP 1% and 2% w/v Solution for Injection (Antigen Pharmaceuticals Limited, Ireland).

As this product is for parenteral use, the requirements for essential similarity of the test and reference products have been met with respect to qualitative and quantitative content of the active substance.

**RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative data support the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with lidocaine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**Lidocaine 1% w/v Solution for Injection (PL 20910/0011)**  
**Lidocaine 2% w/v Solution for Injection (PL 20910/0012)**

**STEPS TAKEN FOR ASSESMENT**

|   |   |
|---|---|
| 1 | The MHRA received the marketing authorisation applications on 31 <sup>st</sup> October 2005   |
| 2 | Following standard checks and communication with the applicant the MHRA considered the applications valid on 7 <sup>th</sup> November 2005  |
| 3 | Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 29 <sup>th</sup> March 2006, 11 <sup>th</sup> December 2006 and 4 <sup>th</sup> July 2007 |
| 4 | The applicant responded to the MHRA's requests, providing further information on 27 <sup>th</sup> August 2006, 9 <sup>th</sup> May 2007 and 16 <sup>th</sup> July 2007 for the quality sections.              |
| 5 | The applications were determined on 15 <sup>th</sup> August 2007  |

**Lidocaine 1% w/v Solution for Injection (PL 20910/0011)**  
**Lidocaine 2% w/v Solution for Injection (PL 20910/0012)**

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

| <b>Date submitted</b> | <b>Application type</b> | <b>Scope</b> | <b>Outcome</b> |
|-----------------------|-------------------------|--------------|----------------|
|                       |                         |              |                |
|                       |                         |              |                |
|                       |                         |              |                |
|                       |                         |              |                |
|                       |                         |              |                |

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Lidocaine 1% w/v solution for injection.

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution for injection contains 10 mg lidocaine hydrochloride.

Each 5 ml of solution contains 50 mg lidocaine hydrochloride.

Each 10 ml of solution for injection contains 100 mg lidocaine hydrochloride.

For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Lidocaine is a local anaesthetic of the amide group. Lidocaine solution for injection is indicated for use in infiltration anaesthesia, intravenous regional anaesthesia and nerve blocks.

#### 4.2 Posology and method of administration

The method of administration of lidocaine varies according to the procedure (infiltration anaesthesia, intravenous regional anaesthesia or nerve block).

The dosage should be adjusted according to the response of the patient and the site of administration. The lowest concentration and smallest dose producing the required effect should be given. The dosage varies depending on the area to be anaesthetised, vascularity of the tissues, number of neuronal segments to be blocked, individual tolerance and the anaesthetic technique. The lowest dosage needed to provide anaesthesia should be administered.

Unnecessarily high doses of local anaesthetics are to be avoided. In general, surgical anaesthesia (e.g. epidural administration) requires the use of higher concentrations and doses. When blocking smaller nerves, or when a less intense block is required, the use of a lower concentration is indicated. The volume of drug used will affect the extent and spread of anaesthesia. The maximum dose for healthy adults should not exceed 200 mg.

Care should be taken to prevent acute toxic reactions by avoiding intravascular injection. Careful aspiration before and during the injection is recommended. When a large dose is to be injected, e.g. in epidural block, a test dose of 3 – 5 ml of lidocaine containing adrenaline (epinephrine) is recommended. An accidental intravascular injection may be recognised by a temporary increase in heart rate. The main dose should be injected slowly while keeping in constant verbal contact with the patient. If toxic symptoms occur, the injection should be stopped immediately.

Children: The dosage should be calculated on a weight basis and should not exceed 5 mg/kg.

Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

#### 4.3 Contraindications

Known hypersensitivity to anaesthetics of the amide type or to any of the excipients in the injection.

#### 4.4 Special warnings and precautions for use

As with other local anaesthetics, lidocaine should be used with caution in patients with epilepsy, impaired cardiac conduction, congestive cardiac failure, bradycardia or impaired respiratory function, if the dose or site of administration is likely to produce high blood levels. Lidocaine is metabolised in the liver and it should be used with caution in patients with impaired hepatic function.

Facilities for resuscitation should be available when administering local anaesthetics.

The effect of local anaesthetics may be reduced if the injection is made into an inflamed or infected area.

Solutions containing adrenaline should be used with caution in patients with hypertension, cardiac disease, cerebrovascular insufficiency, thyrotoxicosis, in patients taking tricyclic antidepressants, MAOI's or receiving potent anaesthetic agents.

Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of the local anaesthetic drug used, e.g.:

Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia, and therefore epidural anaesthesia should be used with caution in patients with impaired cardiovascular function.

Retrobulbar injections may rarely reach the cranial subarachnoid space, causing serious / severe reactions, including cardiovascular collapse, apnoea, convulsions and temporary blindness.

Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/or nerves.

The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used.

Injections in the head and neck regions may be made inadvertently into an artery, causing cerebral symptoms even at low doses.

Paracervical block can sometimes cause foetal bradycardia/tachycardia, and careful monitoring of the foetal heart rate is necessary.

Epidural anaesthesia may lead to hypotension and bradycardia. This risk can be reduced by preloading the circulation with crystalloidal or colloidal solutions. Hypotension should be treated promptly with e.g. ephedrine 5-10 mg intravenously and repeated as necessary.

Each 5 ml of Lidocaine 1% w/v solution for injection contains approximately 13.57 mg (0.59 mmol) sodium.

Each 10 ml of Lidocaine 1% w/v solution for injection contains approximately 27.14 mg (1.18 mmol) sodium.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The speed of onset and duration of action of lidocaine are increased by the addition of a vasoconstrictor such as adrenaline and absorption from the site of injection is reduced.

Dopamine and 5-hydroxytryptamine depletion both reduce the convulsant threshold of lidocaine, and the concomitant use of pethidine increases the incidence of lidocaine-induced convulsions in animals.

Cimetidine and propranolol depress microsomal enzyme activity, thus enhancing lidocaine toxicity during anti-arrhythmic infusions if concomitantly administered with these drugs. Opioid-antiemetic combination sometimes used for sedation in children could reduce the convulsant threshold to lignocaine and increase the CNS depressant effect.

While adrenaline (epinephrine) when used in conjunction with lidocaine might decrease vascular absorption, it greatly increases the danger of ventricular tachycardia and fibrillation if accidentally injected intravenously.

Cardiovascular collapse has been reported following the use of bupivacaine in patients on treatment with verapamil and timolol; lidocaine is closely related to bupivacaine.

**4.6 Pregnancy and lactation**

Although animal studies have revealed no evidence of harm to the foetus, lidocaine should not be administered during early pregnancy unless the benefits are considered to outweigh the risks.

Small amounts of lidocaine are secreted into breast milk and the possibility of an allergic reaction in the infant, albeit remote, should be borne in mind when using lidocaine in nursing mothers.

**4.7 Effects on ability to drive and use machines**

Where outpatient anaesthesia affects areas of the body involved in driving or operating machinery, patients should be advised to avoid these activities until normal function is fully restored.

**4.8 Undesirable effects**

In common with other local anaesthetics, adverse reactions to lidocaine are rare and are usually the result of raised plasma concentrations due to accidental intravascular injection, excessive dosage or rapid absorption from highly vascular areas, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Systemic toxicity mainly involves the central nervous system and/or the cardiovascular system.

CNS reactions may be excitatory and/or depressant and may manifest as nervousness, tremor, blurred vision, nausea and vomiting, followed by drowsiness, coma and possibly respiratory arrest. The excitatory reactions may be brief or may not occur at all, so that the first signs of toxicity may be drowsiness, followed by coma and respiratory failure. Cardiovascular reactions are depressant and may manifest as hypotension, bradycardia, myocardial depression and possibly cardiac arrest.

Allergic reactions are rare. They may be characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions. Skin testing for allergy to lidocaine is not considered to be reliable.

Localised nerve damage at the site of injection (very rare).

Prolonged neural blockade following epidural may be due to delayed spread. Permanent neural blockade may be more likely associated with hypotension and cord ischaemia.

Following regional blockade as when lidocaine is injected intrathecally or extradurally, hypotension, hypoventilation, Horner's Syndrome and hypoglycaemia may be seen. The degree of these effects will depend on the dose and the height of the block. Urinary retention may occur following sacral or lumbar epidural block. It should not outlast the duration of the block. Apnoea and coma followed by aphasia and hemiparesis may occur following stellate ganglion block. The probable cause is a direct injection of lidocaine into the vertebral or carotid arteries.

Profound lethargy and death have been reported following the injection of only 10 – 32 mg of lidocaine for dental blocks.

Diplopia and temporary blindness has been reported following lidocaine for maxillary block, also respiratory arrest following retrobulbar block.

The major adverse effects on the CNS and CVS are primarily due to the absorption of lidocaine into the systemic circulation. Lidocaine may also produce methaemoglobinaemia.

The initial CNS toxic effects are demonstrated by a gradual onset of drowsiness or inebriation similar to alcoholic intoxication. Balance is disturbed, circumoral pins and needles, numb tongue, roaring in the ears, visual disturbances, restlessness and twitching may occur. Severe intoxication of rapid onset may immediately lead to convulsions followed by circulatory depression. Major overdosage may depress all systems simultaneously. Psychotic reactions have been reported following infusion for the control of arrhythmia.



Profound hypotension may be associated with B blockade, widespread sympathetic block from spinal or epidural block, intercostal nerve block administration or supine hypotension in pregnancy.

Ventricular fibrillation occurs less frequently than that seen with bupivacaine.

#### **4.9 Overdose**

The effects of overdosage involve the CNS, where reactions may be excitatory and/or depressant, and the CVS where the effects are depressant. In the event of an overdose, immediate steps should be taken to maintain the circulation and respiration and to control convulsions.

A patent airway should be established and oxygen should be administered, together with assisted ventilation if necessary. The circulation should be maintained with infusions of plasma or intravenous fluids. Where further supportive treatment of circulatory depression is required, use of a vasopressor agent may be considered although this involves a risk of CNS excitation. Convulsions may be controlled by the intravenous administration of diazepam or thiopentone sodium, bearing in mind that anti-convulsant drugs may also depress respiration and the circulation. If cardiac arrest should occur, standard cardiopulmonary resuscitation procedures should be instituted.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

ATC Code:N01BB02

Lidocaine is a local anaesthetic of the amide type. It is used to provide local anaesthesia at various sites in the body and it acts by inhibiting the ionic reflexes required for the initiation and conduction of impulses, thereby stabilising the neuronal membrane. In addition to blocking conduction in nerve axons in the peripheral nervous system, lidocaine has important effects on the central nervous system and cardiovascular system. After absorption, lidocaine may cause stimulation of the CNS followed by depression and in the cardiovascular system, it acts primarily on the myocardium where it may produce decreases in electrical excitability, conduction rate and force of contraction.

### **5.2 Pharmacokinetic properties**

Lidocaine is absorbed from injection sites including muscle and its rate of absorption is determined by factors such as the site of administration and the tissue vascularity. Except for intravascular administration, the highest blood levels occur following intercostal nerve block and the lowest after subcutaneous administration. Lidocaine is bound to plasma proteins, including alpha-1-acid-glycoprotein. The drug crosses the blood-brain and placental barriers.

Lidocaine is metabolised in the liver and about 90% of a given dose undergoes N-dealkylation to form monoethylglycinexylidide and glycinexylidide, both of which may contribute to the therapeutic and toxic effects of lidocaine. Further metabolism occurs and metabolites are excreted in the urine with less than 10% as unchanged lidocaine.

The elimination half-life of lidocaine following an intravenous bolus injection is one to two hours, but this may be prolonged in patients with hepatic dysfunction.

### **5.3 Preclinical safety data**

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

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium Chloride  
Sodium Hydroxide  
Hydrochloric Acid  
Water for Injections

- 6.2 Incompatibilities**  
Lidocaine solution for injection should not be mixed with other preparations unless compatibility is known.
- 6.3 Shelf life**  
Unopened: 2 years.
- 6.4 Special precautions for storage**  
Do not store above 25°C.
- 6.5 Nature and contents of container**  
5 ml and 10 ml translucent polypropylene ampoules  
Pack sizes: 20 x 5 ml  
20 x 10 ml
- 6.6 Special precautions for disposal and other handling**  
Use as directed by the physician.  
Keep out of the reach and sight of children.  
For single use only.  
Use immediately after opening.  
If only part of an ampoule is used, discard the remaining solution.  
The injection should not be used if particles are present.
- 7 MARKETING AUTHORISATION HOLDER**  
Taro Pharmaceuticals Ireland Ltd.,  
Lourdes Road,  
Roscrea,  
County Tipperary,  
Ireland.
- 8 MARKETING AUTHORISATION NUMBER(S)**  
PL 20910/0011
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
15/08/2007
- 10 DATE OF REVISION OF THE TEXT**

**1 NAME OF THE MEDICINAL PRODUCT**

Lidocaine 2% w/v solution for injection

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 1 ml of solution for injection contains 20 mg lidocaine hydrochloride.

Each 5 ml of solution contains 100 mg lidocaine hydrochloride.

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Solution for injection.

Clear, colourless solution

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications**

Lidocaine is a local anaesthetic of the amide group. Lidocaine solution for injection is indicated for use in infiltration anaesthesia, intravenous regional anaesthesia and nerve blocks.

**4.2 Posology and method of administration**

The method of administration of lidocaine varies according to the procedure (infiltration anaesthesia, intravenous regional anaesthesia or nerve block).

The dosage should be adjusted according to the response of the patient and the site of administration. The lowest concentration and smallest dose producing the required effect should be given. The dosage varies depending on the area to be anaesthetised, vascularity of the tissues, number of neuronal segments to be blocked, individual tolerance and the anaesthetic technique. The lowest dosage needed to provide anaesthesia should be administered.

Unnecessarily high doses of local anaesthetics are to be avoided. In general, surgical anaesthesia (e.g. epidural administration) requires the use of higher concentrations and doses. When blocking smaller nerves, or when a less intense block is required, the use of a lower concentration is indicated. The volume of drug used will affect the extent and spread of anaesthesia. The maximum dose for healthy adults should not exceed 200 mg.

Care should be taken to prevent acute toxic reactions by avoiding intravascular injection. Careful aspiration before and during the injection is recommended. When a large dose is to be injected, e.g. in epidural block, a test dose of 3 – 5 ml of lidocaine containing adrenaline (epinephrine) is recommended. An accidental intravascular injection may be recognised by a temporary increase in heart rate. The main dose should be injected slowly while keeping in constant verbal contact with the patient. If toxic symptoms occur, the injection should be stopped immediately.

Children: The dosage should be calculated on a weight basis and should not exceed 5 mg/kg.

Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

**4.3 Contraindications**

Known hypersensitivity to anaesthetics of the amide type or to any of the excipients in the injection.

**4.4 Special warnings and precautions for use**

As with other local anaesthetics, lidocaine should be used with caution in patients with epilepsy, impaired cardiac conduction, congestive cardiac failure, bradycardia or impaired respiratory function, if the dose or site of administration is likely to produce high blood levels. Lidocaine is metabolised in the liver and it should be used with caution in patients with impaired hepatic function.

Facilities for resuscitation should be available when administering local anaesthetics.

The effect of local anaesthetics may be reduced if the injection is made into an inflamed or infected area.

Solutions containing adrenaline should be used with caution in patients with hypertension, cardiac disease, cerebrovascular insufficiency, thyrotoxicosis, in patients taking tricyclic antidepressants, MAOI's or receiving potent anaesthetic agents.

Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of the local anaesthetic drug used, e.g.:

- Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia, and therefore epidural anaesthesia should be used with caution in patients with impaired cardiovascular function.
- Retrobulbar injections may rarely reach the cranial subarachnoid space, causing serious / severe reactions, including cardiovascular collapse, apnoea, convulsions and temporary blindness.
- Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/or nerves.

The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used.

- Injections in the head and neck regions may be made inadvertently into an artery, causing cerebral symptoms even at low doses.
- Paracervical block can sometimes cause foetal bradycardia/tachycardia, and careful monitoring of the foetal heart rate is necessary.

Epidural anaesthesia may lead to hypotension and bradycardia. This risk can be reduced by preloading the circulation with crystalloidal or colloidal solutions. Hypotension should be treated promptly with e.g. ephedrine 5-10 mg intravenously and repeated as necessary.

Each 5 ml of Lidocaine 2% w/v solution for injection contains approximately 9.44 mg (0.41 mmol) sodium.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The speed of onset and duration of action of lidocaine are increased by the addition of a vasoconstrictor such as adrenaline and absorption from the site of injection is reduced.

Dopamine and 5-hydroxytryptamine depletion both reduce the convulsant threshold of lidocaine, and the concomitant use of pethidine increases the incidence of lidocaine-induced convulsions in animals.

Cimetidine and propranolol depress microsomal enzyme activity, thus enhancing lidocaine toxicity during anti-arrhythmic infusions if concomitantly administered with these drugs.

Opioid-antiemetic combination sometimes used for sedation in children could reduce the convulsant threshold to lignocaine and increase the CNS depressant effect.

While adrenaline (epinephrine) when used in conjunction with lidocaine might decrease vascular absorption, it greatly increases the danger of ventricular tachycardia and fibrillation if accidentally injected intravenously.

Cardiovascular collapse has been reported following the use of bupivacaine in patients on treatment with verapamil and timolol; lidocaine is closely related to bupivacaine.

#### **4.6 Pregnancy and lactation**

Although animal studies have revealed no evidence of harm to the foetus, lidocaine should not be administered during early pregnancy unless the benefits are considered to outweigh the risks.

Small amounts of lidocaine are secreted into breast milk and the possibility of an allergic reaction in the infant, albeit remote, should be borne in mind when using lidocaine in nursing mothers.

#### 4.7 **Effects on ability to drive and use machines**

Where outpatient anaesthesia affects areas of the body involved in driving or operating machinery, patients should be advised to avoid these activities until normal function is fully restored.

#### 4.8 **Undesirable effects**

In common with other local anaesthetics, adverse reactions to lidocaine are rare and are usually the result of raised plasma concentrations due to accidental intravascular injection, excessive dosage or rapid absorption from highly vascular areas, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Systemic toxicity mainly involves the central nervous system and/or the cardiovascular system.

CNS reactions may be excitatory and/or depressant and may manifest as nervousness, tremor, blurred vision, nausea and vomiting, followed by drowsiness, coma and possibly respiratory arrest. The excitatory reactions may be brief or may not occur at all, so that the first signs of toxicity may be drowsiness, followed by coma and respiratory failure. Cardiovascular reactions are depressant and may manifest as hypotension, bradycardia, myocardial depression and possibly cardiac arrest.

Allergic reactions are rare. They may be characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions. Skin testing for allergy to lidocaine is not considered to be reliable.

Localised nerve damage at the site of injection (very rare).

Prolonged neural blockade following epidural may be due to delayed spread. Permanent neural blockade may be more likely associated with hypotension and cord ischaemia.

Following regional blockade as when lidocaine is injected intrathecally or extradurally, hypotension, hypoventilation, Horner's Syndrome and hypoglycaemia may be seen. The degree of these effects will depend on the dose and the height of the block. Urinary retention may occur following sacral or lumbar epidural block. It should not outlast the duration of the block. Apnoea and coma followed by aphasia and hemiparesis may occur following stellate ganglion block. The probable cause is a direct injection of lidocaine into the vertebral or carotid arteries.

Profound lethargy and death have been reported following the injection of only 10 – 32 mg of lidocaine for dental blocks.

Diplopia and temporary blindness has been reported following lidocaine for maxillary block, also respiratory arrest following retrobulbar block.

The major adverse effects on the CNS and CVS are primarily due to the absorption of lidocaine into the systemic circulation. Lidocaine may also produce methaemoglobinaemia.

The initial CNS toxic effects are demonstrated by a gradual onset of drowsiness or inebriation similar to alcoholic intoxication. Balance is disturbed, circumoral pins and needles, numb tongue, roaring in the ears, visual disturbances, restlessness and twitching may occur. Severe intoxication of rapid onset may immediately lead to convulsions followed by circulatory depression. Major overdosage may depress all systems simultaneously. Psychotic reactions have been reported following infusion for the control of arrhythmia.

Profound hypotension may be associated with B blockade, widespread sympathetic block from spinal or epidural block, intercostal nerve block administration or supine hypotension in pregnancy.

Ventricular fibrillation occurs less frequently than that seen with bupivacaine.

**4.9 Overdose**

The effects of overdosage involve the CNS, where reactions may be excitatory and/or depressant, and the CVS where the effects are depressant. In the event of an overdose, immediate steps should be taken to maintain the circulation and respiration and to control convulsions.

A patent airway should be established and oxygen should be administered, together with assisted ventilation if necessary. The circulation should be maintained with infusions of plasma or intravenous fluids. Where further supportive treatment of circulatory depression is required, use of a vasopressor agent may be considered although this involves a risk of CNS excitation. Convulsions may be controlled by the intravenous administration of diazepam or thiopentone sodium, bearing in mind that anti-convulsant drugs may also depress respiration and the circulation. If cardiac arrest should occur, standard cardiopulmonary resuscitation procedures should be instituted.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

**5 PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

ATC Code:N01BB02

Lidocaine is a local anaesthetic of the amide type. It is used to provide local anaesthesia at various sites in the body and it acts by inhibiting the ionic reflexes required for the initiation and conduction of impulses, thereby stabilising the neuronal membrane. In addition to blocking conduction in nerve axons in the peripheral nervous system, lidocaine has important effects on the central nervous system and cardiovascular system. After absorption, lidocaine may cause stimulation of the CNS followed by depression and in the cardiovascular system, it acts primarily on the myocardium where it may produce decreases in electrical excitability, conduction rate and force of contraction.

**5.2 Pharmacokinetic properties**

Lidocaine is absorbed from injection sites including muscle and its rate of absorption is determined by factors such as the site of administration and the tissue vascularity. Except for intravascular administration, the highest blood levels occur following intercostal nerve block and the lowest after subcutaneous administration. Lidocaine is bound to plasma proteins, including alpha-1-acid-glycoprotein. The drug crosses the blood-brain and placental barriers.

Lidocaine is metabolised in the liver and about 90% of a given dose undergoes N-dealkylation to form monoethylglycinexylidide and glycinexylidide, both of which may contribute to the therapeutic and toxic effects of lidocaine. Further metabolism occurs and metabolites are excreted in the urine with less than 10% as unchanged lidocaine.

The elimination half-life of lidocaine following an intravenous bolus injection is one to two hours, but this may be prolonged in patients with hepatic dysfunction.

**5.3 Preclinical safety data**

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

**6 PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

Sodium Chloride  
Sodium Hydroxide  
Hydrochloric Acid  
Water for Injections

**6.2 Incompatibilities**

Lidocaine solution for injection should not be mixed with other preparations unless compatibility is known.

**6.3 Shelf life**

Unopened: 2 years.

- 6.4 Special precautions for storage**  
Do not store above 25°C.
- 6.5 Nature and contents of container**  
5 ml translucent polypropylene ampoules  
Pack size: 20 x 5 ml
- 6.6 Special precautions for disposal and other handling**  
Use as directed by the physician.  
Keep out of the reach and sight of children.  
For single use only.  
Use immediately after opening.  
If only part of an ampoule is used, discard the remaining solution.  
The injection should not be used if particles are present.
- 7 MARKETING AUTHORISATION HOLDER**  
Taro Pharmaceuticals Ireland Ltd.,  
Lourdes Road,  
Roscrea,  
County Tipperary,  
Ireland.
- 8 MARKETING AUTHORISATION NUMBER(S)**  
PL 20910/0012
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**  
15/08/2007
- 10 DATE OF REVISION OF THE TEXT**  
15/08/2007

**PACKAGE LEAFLET: INFORMATION FOR THE USER**  
**Lidocaine 1% w/v, 2% w/v solution for injection**  
**Lidocaine Hydrochloride**

PR0000-00

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

**In this leaflet:**

1. What Lidocaine solution for injection is and what it is used for
2. Before you use Lidocaine solution for injection
3. How to use Lidocaine solution for injection
4. Possible side effects
5. How to store Lidocaine solution for injection
6. Further information

**1. WHAT LIDOCAINE SOLUTION FOR INJECTION IS AND WHAT IT IS USED FOR**

Lidocaine hydrochloride is a local anaesthetic. These are medicines which numb an area of the body. Lidocaine belongs to a group of medicines called amide-type local anaesthetics. It produces a loss of feeling or sensation that is confined to one part of the body (local anaesthesia).

Lidocaine solution for injection is used to numb specific parts of the body and prevent pain during medical procedures or surgery.

**2. BEFORE YOU USE LIDOCAINE SOLUTION FOR INJECTION****Do not use Lidocaine solution for injection**

- If you are hypersensitive (allergic) to lidocaine or local anaesthetics of the amide type or to any of the other ingredients in this medicine. An allergic reaction may be recognised as a rash, itching, swollen face or lips, or shortness of breath.

**Take special care with Lidocaine solution for injection**

- if you suffer from epilepsy
- if you have any heart problems, in particular a slow heartbeat
- if you have problems with your breathing
- if you suffer from any liver disorder
- if you have any inflammation or infection in the area to be injected
- if you have been told that you have reduced levels of the body chemicals dopamine and 5-hydroxytryptamine (serotonin).

You should talk to your doctor if you think this could apply to you.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium free.

**Taking other medicines**

Please inform your doctor if you are taking any medicines, even those not prescribed. Taking some medicines together can be harmful. Remember that the doctor at the hospital may not have been informed if you have recently begun a course of treatment for another illness. In particular tell your doctor if you are taking

- other local anaesthetics
- volatile anaesthetics e.g. chloroform, halothane, cyclopropane, trichlorethylene, or other related agents
- pethidine (strong pain reliever)
- cimetidine (for stomach problems)
- betablockers which are used to control your heart beat or to lower your blood pressure e.g. propranolol
- antidepressant drugs.

If adrenaline (epinephrine) is to be added to your Lidocaine solution for injection, you should tell your doctor if you suffer from high blood pressure, shortage of blood supply to the brain, an overactive thyroid gland or if you are taking antidepressant drugs.

**Pregnancy and breast-feeding**

If you are pregnant or you think you may be pregnant, you should inform your doctor who will decide whether or not you should be given lidocaine. Ask your doctor or pharmacist for advice before taking any medicine.

Lidocaine may get into breast milk. If you are breast-feeding you should discuss options with your doctor. Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**

Do not drive or use any tools or machines because lidocaine may interfere with your ability to do so safely. Ask your doctor when it would be safe to resume these activities.

**3. HOW TO USE LIDOCAINE SOLUTION FOR INJECTION**

Lidocaine solution for injection may be used to produce local anaesthesia by injection of the solution into or around a peripheral nerve or network of nerves. It may also be used to relieve pain by administering the solution into the epidural space, which is close to the spinal cord, or into a vein in a limb that has been isolated from the circulation by means of a tourniquet. If you are unsure why you have been given this product and how to use it, ask your doctor to explain.



Your doctor will decide what dose is right for you. The maximum dose for healthy adults should not exceed 200 mg. The dose will depend on your size, your state of health, the part of the body that the medicine is injected into and what the medicine is being used for. Smaller doses are used for elderly people, young children and people who are unwell. The dose for children should not exceed 5 mg per kg bodyweight.

For most procedures, one dose is enough but more doses may be needed if the procedure takes a long time.

**If you use more Lidocaine solution for injection than you should**

If you think you have been given too much of this medicine, tell your doctor.

**If you miss a dose of Lidocaine solution for injection**

If you think you have missed a dose of this medicine, tell your doctor.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Lidocaine solution for injection may have side effects. Lidocaine is generally well tolerated. Serious side effects are rare and usually only occur with high blood levels of lidocaine. Tell your doctor immediately if you notice any of the following

- any signs of an allergic reaction such as a skin rash, wheeziness, swelling of the tongue or lips, or feeling suddenly weak and unwell (allergic reactions to lidocaine are rare)
- numbness of the tongue, feeling dizzy and light-headed, blurred vision, muscle twitching, drowsiness and occasionally loss of consciousness, fits, low blood pressure and slowed breathing or heart beat which may be life threatening (these symptoms are suggestive of too much lidocaine entering the blood stream)
- yellowing of the skin or the white of the eyes (signs of disturbed liver function, which are reversible, have been observed after repeated administration of lidocaine).

Nerve damage can rarely occur with some types of nerve block and may result in localised areas of anaesthesia or paraesthesia (tingling or other odd sensations), loss of bladder control or loss of power in the legs. These effects may be permanent.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

**5. HOW TO STORE LIDOCAINE SOLUTION FOR INJECTION**

Keep out of the reach and sight of children.

Do not store above 25°C.

Do not use after the expiry date stated on the ampoule and carton.

For single use only.

Discard any unused contents.

The product should be used immediately after opening.

Do not use the ampoule if the contents are discoloured in any way.

The injection should not be used if there are particles present.

**6. FURTHER INFORMATION**

**What Lidocaine solution for injection contains**

The active substance is lidocaine hydrochloride.

The other ingredients are sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

**What Lidocaine solution for injection looks like and the contents of the pack**

Lidocaine solution for injection is a clear, colourless, sterile solution for injection. It is available in two strengths, 1% w/v and 2% w/v.

Lidocaine 1% w/v solution for injection: Each 1 ml of solution contains 10 mg of lidocaine hydrochloride. Lidocaine 1% w/v solution for injection is available in 5 ml and 10 ml polypropylene ampoules packed in cartons of 20 ampoules.

Lidocaine 2% w/v solution for injection: Each 1 ml of solution contains 20 mg of lidocaine hydrochloride. Lidocaine 2% w/v solution for injection is available in 5 ml polypropylene ampoules packed in cartons of 20 ampoules.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Taro Pharmaceuticals Ireland Ltd.,

Lourdes Road,

Roscrea,

County Tipperary,

Ireland.

Tel: + 353 (0) 505 24300

Fax: + 353 (0) 505 24310

info@taro.ie

For any further information about this medicinal product, please contact the Marketing Authorisation Holder.

This leaflet was last approved in MM/YYYY

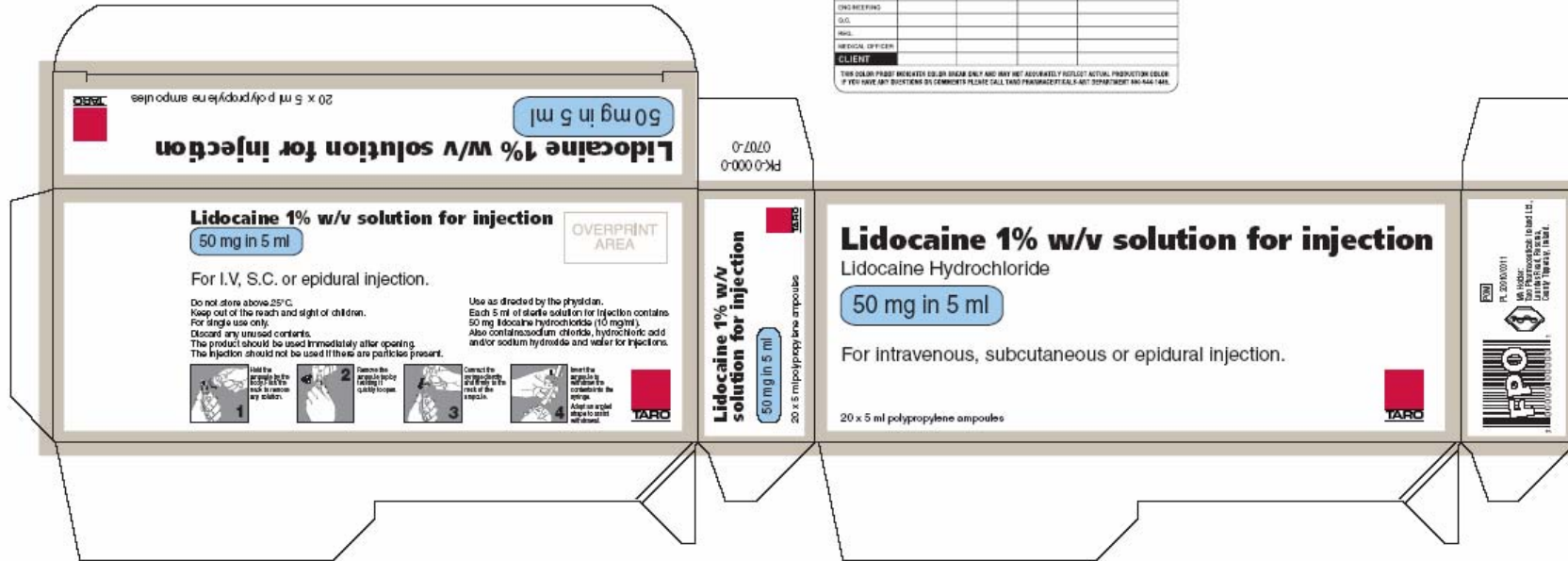


DPL 946  
 20 X 5ml  
 187 x 34 x 73mm

  
 PMS 283    Black    PMS 200    PMS 401

| APPROVAL        |                    |      |               |
|-----------------|--------------------|------|---------------|
| DATE            | 7/8/07             | PEP  | 0000-0        |
| PAPER           | DL-0014-NCB-14001E | UPCF | PHARMACOP 010 |
| DEPARTMENT      | SIGNATURE          | NO   | YES           |
| PREP'ING        |                    |      |               |
| ASST            |                    |      |               |
| REPORTING       |                    |      |               |
| ENGINEERING     |                    |      |               |
| D.C.            |                    |      |               |
| MSL             |                    |      |               |
| MEDICAL OFFICER |                    |      |               |
| CLIENT          |                    |      |               |

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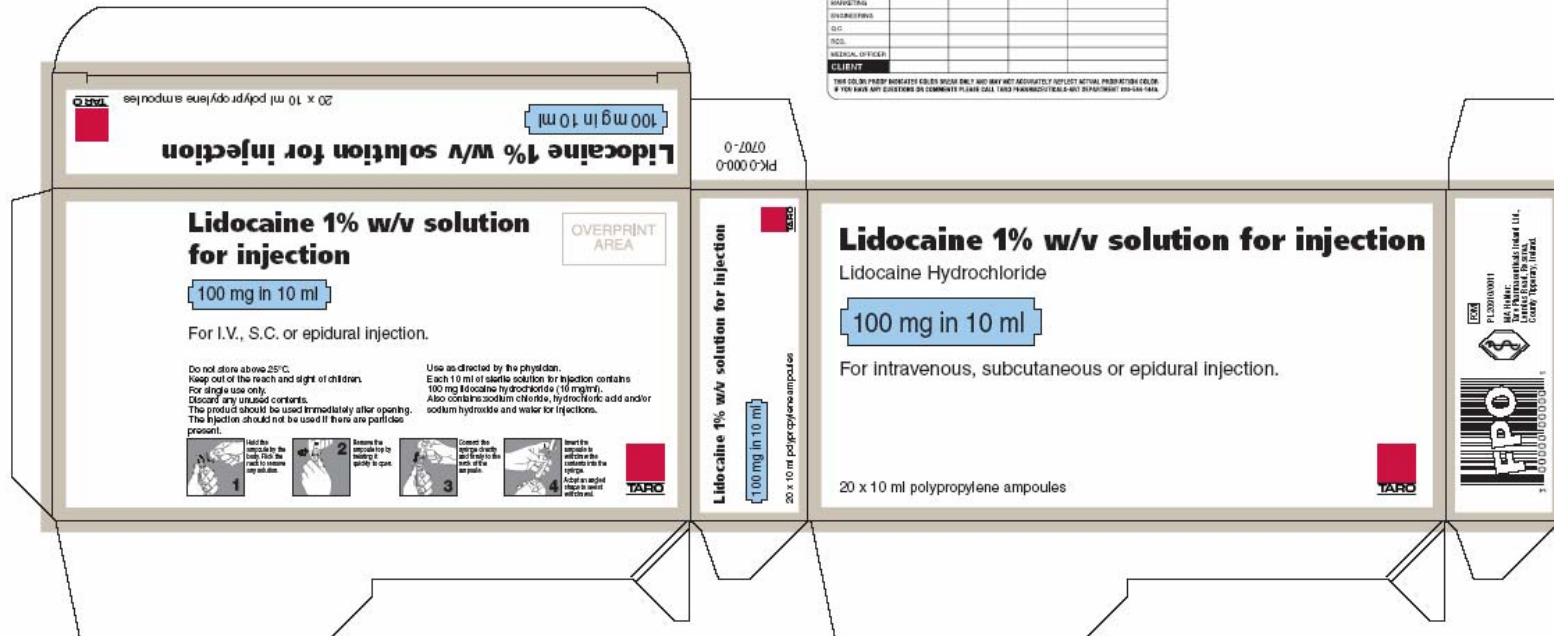
**Lidocaine** Taro  
**1% w/v Injection** 50 mg in 5 ml  
 Lidocaine Hydrochloride  
 For IV, SC or epidural use. 5 ml

DPL 379  
TARO - 20 x 10ml  
187 x 34 x 97mm

  
PMS 283    Black    PMS 200    PMS 401

| APPROVAL        |                   |      |        |                 |
|-----------------|-------------------|------|--------|-----------------|
| DATE            | 7/1/07            | PK#  | 1010-0 | ART COPY CTRL#  |
| PAGE#           | EE-001-418-TAR00F | UPC# |        | PHARMACODUM 010 |
| DEPARTMENT      | SIGNATURE         | NO.  | YR     | DATE            |
| PRODUCTION      |                   |      |        |                 |
| QA              |                   |      |        |                 |
| MARKETING       |                   |      |        |                 |
| REGISTRATION    |                   |      |        |                 |
| SEC.            |                   |      |        |                 |
| RES.            |                   |      |        |                 |
| MEDICAL OFFICER |                   |      |        |                 |

THE COLOR FROM THESE COLORS SHOULD ONLY BE USED TO ACCURATELY REPRODUCE ACTUAL PRODUCTION COLOR. IF YOU HAVE ANY QUESTIONS OR COMMENTS PLEASE CALL TARO PHARMACEUTICALS-NEW BRANFORD 203-583-1818



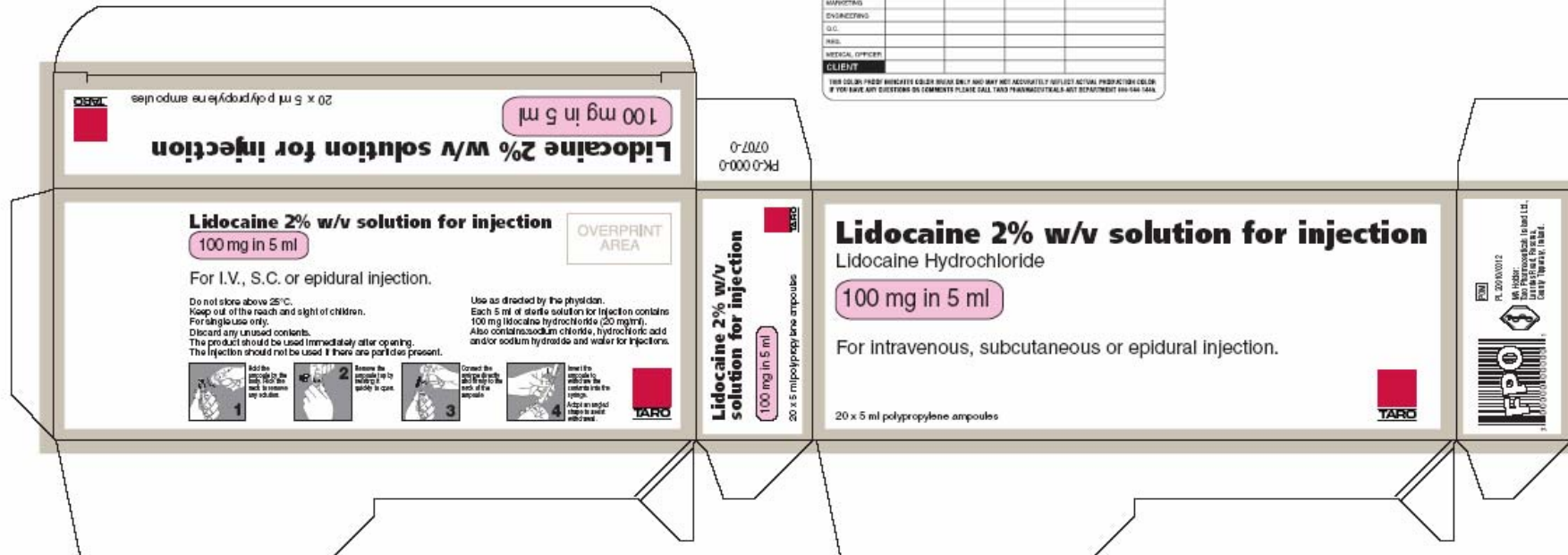
|  |       |
|--|-------|
| <b>Lidocaine 1% w/v Injection</b>              | Taro  |
| Lidocaine Hydrochloride <b>100 mg in 10 ml</b> |       |
| For IV, SC or epidural use.                    | 10 ml |

DPL 946  
20 X 5ml  
187 x 34 x 73mm



| APPROVAL        |                      |      |        |                |
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| DATE            | 7/8/07               | REF  | 1010-0 | ART COPY CTRL# |
| PASS#           | 06-0001-0001-TARO00E | UPC# |        | PHARMACOSM 010 |
| DEPARTMENT      | SIGNATURE            | NO   | YES    | DATE           |
| PRODUCTION      |                      |      |        |                |
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| MARKETING       |                      |      |        |                |
| ENGINEERING     |                      |      |        |                |
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| MEDICAL OFFICER |                      |      |        |                |
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**Lidocaine** Taro  
**2% w/v Injection** (100 mg in 5 ml)  
Lidocaine Hydrochloride  
For IV, SC or epidural use. 5 ml