The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 19 December 2000
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EMEA PUBLIC STATEMENT ON LEVACETYLMETHADOL (ORLAAM) - LIFE THREATENING VENTRICULAR RHYTHM DISORDERS

The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP) has been made aware of 10 case reports of life-threatening cardiac disorders including ventricular rhythm disorders such as Torsades de pointes in patients treated with Orlaam (levacethylmethadol).

Orlaam[1] is indicated for the substitution maintenance treatment of opiate addiction in adults previously treated with methadone, as part of a comprehensive treatment plan including medical, social and psychological care. Orlaam is currently marketed in the EU in **Denmark, Germany, The Netherlands, Portugal, Spain and United Kingdom.** This product has been made available in the USA since 1994.

These 10 cases of life-threatening cardiac rhythm disorders have been reported since 1 July 1997. They include 5 cases of cardiac arrest associated with ventricular arrhythmias, 3 cases of cardiac arrhythmia and 2 cases of syncope. The QT interval was prolonged in 7 of the patients (from 535 msec to 800 msec) and 4 of these patients had an episode of Torsade de pointes. Finally 3 patients required a pacemaker insertion. This raises a major concern given the fact that these life-threatening cases occurred in young patients (median age is 39 years old [range: from 23 to 57 years old]), a population at low risk of developing these cardiac disorders, and given the relatively low exposure to the product. Furthermore these cardiac disorders might have been under-recognised or under-reported.

Following a preliminary review of this new safety information, as an interim and precautionary measure while the CPMP performs a full comparative risk/benefit re-assessment of Orlaam, the EMEA wishes to draw attention to the following:

- **PRESCRIBERS ARE ADVISED NOT TO INTRODUCE ANY NEW PATIENTS TO ORLAAM THERAPY.**
- **Patients currently taking Orlaam should contact their doctor for advice regarding their treatment, they must not stop Orlaam suddenly without seeking medical advice.**

The attention of prescribers is drawn to the special warnings and precautions for use concerning the assessment of the risk of Torsade de pointes. The complete product information for Orlaam, (Summary of Product Characteristics and Package Leaflet) is annexed to this Public Statement.

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[1] The European Commission granted a marketing authorisation for the European Union to Sipaco Internacional Lda. on 1 July 1997 for the medicinal product ORLAAM, which contains the active substance levacetylmethadol.

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ORLAAM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle of 120 ml and 500 ml of ORLAAM contains 10 mg/ml levacetylmethadol hydrochloride in a solution.

3. PHARMACEUTICAL FORM

Oral solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ORLAAM is indicated for the substitution maintenance treatment of opiate addiction in adults previously treated with methadone, as part of a comprehensive treatment plan including medical, social and psychological care.

ORLAAM should be administered under the supervision of physicians with experience in addiction treatment and whenever practicable, in centres specialising in the treatment of drug addiction.

ORLAAM is not intended for take home use.

4.2 Posology and method of administration

Dosing Schedules:
The recommended doses are intended for every-other-day or 3-times-a-week dosing, usually either on Monday, Wednesday and Friday, or on Tuesday, Thursday and Saturday.

In some patients, ORLAAM may not provide adequate suppression of withdrawal for a full 72 hours. For such individuals, several therapeutic options are available: (1) extra support and an explanation of the reasons for the effects, (2) increasing the dose given prior to the 72-hour interval (see Maintenance), (3) switching to an every-other-day dosing schedule.

Induction of Treatment:
For the safe and rapid induction of treatment, patients should be started on methadone by titration to an effective dose, then switched to ORLAAM after a few weeks of methadone therapy.

Methadone and ORLAAM should not be used alternatively (e.g. ORLAAM during the weekend). ORLAAM should not be administered daily.

Transfer from Methadone:
The change from methadone to ORLAAM should be accomplished in a single dose; complete transfer to ORLAAM is simpler and preferable to more complex regimens involving escalating doses of ORLAAM and decreasing doses of methadone.

For patients on methadone maintenance whose level of tolerance is known, the recommended initial 3-times-a-week dose of ORLAAM is 1.2 to 1.3 times the daily methadone maintenance dose being replaced. This initial dose should not exceed 120 mg and subsequent doses (usually 5 to 10 mg changes every second or third dose), administered at 48- or 72-hour intervals, should be adjusted according to clinical response.

If more than 48 hours have elapsed since their last methadone dose, patients should be inducted on ORLAAM at a dose determined by clinical and/or toxicological evaluation of the patient by the physician.

Maintenance:
Most patients will be stabilized on doses in the range of 60 to 90 mg, three times a week. In women, higher doses may be required but should be used with caution.

Supplemental dosing over the 72-hour inter-dose interval is rarely needed. If it is necessary to supplement a patient on a Monday/Wednesday/Friday schedule, who complains of withdrawal on Sundays, the recommended dosage adjustment is to increase the Friday dose in 5 or 10 mg increments up to 40% over the Monday/Wednesday dose or to a maximum of 140 mg.

The maximum amount of ORLAAM recommended for any patient on a thrice-weekly schedule is 140-140-140 mg or 130-130-180 mg. Exceptionally it could be 140 mg every other day.

Reinduction Following a Lapse of One ORLAAM Dose:

1) If a patient comes to be dosed on the day following a missed scheduled dose, the schedule for the remainder of the week should just be moved by one day with the same regular doses and normal schedule resumed the following week.

2) If a patient misses one dose and comes on the day of the next scheduled dose, the usual dose will be well tolerated in most instances, although a reduced dose may be appropriate in selected cases.

Reinduction Following a Lapse of More than One ORLAAM Dose:
Patients should be reinducted at an initial dose of 1/2 to 3/4 of their previous ORLAAM dose, followed by increases of 5 to 10 mg every dosing day (48- or 72-hour intervals) until their previous maintenance dose is achieved. Patients who have been off ORLAAM treatment for more than a week (3 doses) should be reinducted.

Transfer from ORLAAM to Methadone:
Patients maintained on ORLAAM may be transferred directly to methadone. It is recommended that methadone be started on a daily dose at 80% of the ORLAAM dose. The initial methadone dose must be given no sooner than 48 hours after the last ORLAAM dose. Subsequent increases or decreases of 5 to 10 mg in the daily methadone dose may be given to control symptoms of withdrawal or, less likely, symptoms of excessive sedation, in accordance with clinical observations.

Detoxification from ORLAAM:
There is limited experience with detoxifying patients from ORLAAM in a systematic manner; both gradual reduction (5 to 10% a week) and abrupt withdrawal schedules have been used successfully. The decision to discontinue ORLAAM therapy should be made as part of a comprehensive treatment plan.

A patient is most likely to remain abstinent if discontinuation of medication is attempted after the achievement of behavioral objectives and is accompanied by appropriate non-pharmacological support.

4.3 Contra-indications

- Hypersensitivity to ORLAAM.
- Moderate to severe respiratory impairment
- Children under 15 years
- Breast feeding (see section 4.6, Use during pregnancy and lactation)
- Pregnancy (see section 4.6, Use during pregnancy and lactation)
- Moderate to severe renal impairment

- Moderate to severe hepatic impairment
- Treatment with narcotic antagonists or agonists / antagonists (except for the treatment of overdosage)
- Treatment with Monoamine Oxidase Inhibitors
- Patients with known or suspected QT prolongation (corrected QT, QTc> 440 ms), e.g. congenital long QT Syndrome, or conditions which may lead to QT prolongation such as:
  - clinically significant bradycardia (less than 50 bpm),
  - any other clinically significant cardiac disease,
  - treatment with Class I and III anti-arrhythmics,
  - concomitant treatment with other medicinal products known to prolong the QT interval. These are also listed under section 4.5 (Interaction with other medicinal products and other forms of interaction),
  - electrolyte imbalance, in particular hypokalaemia or hypomagnesaemia, and medical conditions or concomitant treatment with medicinal products with the potential of inducing such imbalance. These include anorexia, vomiting and diarrhoea.

4.4 Special warnings and special precautions for use

WARNINGS:

ORLAAM is not recommended for any use other than the treatment of opioid dependence.

ORLAAM has only been studied on a thrice-weekly or every-other-day dosing regimen. Routine daily dosing after a patient has been inducted onto ORLAAM treatment is hazardous. Administration of ORLAAM on a daily basis has led to excessive drug accumulation and risk of fatal overdose.

Patients must be warned that the peak activity of ORLAAM is not immediate, and that the combination with other psychoactive drugs, including alcohol, may result in fatal overdose, especially with the first few doses of ORLAAM, either during initiation of treatment or after a lapse in treatment.

Cases of QT prolongation and of severe arrhythmia (torsade de pointes) have been observed during treatment with ORLAAM. In patients in whom the potential benefit of ORLAAM is deemed to outweigh the potential risk of torsade de pointes, an ECG should be performed prior to the initiation and after two weeks of treatment to detect and quantify the effect of ORLAAM on QT interval. Likewise, it is advisable to perform an ECG before increase in posology.

ORLAAM should be discontinued if symptoms such as palpitations, dizziness, syncope or convulsion occur, and the patient should be evaluated for QT prolongation and arrhythmias. Reinduction of treatment should be performed as mentioned in section 4.2 (Posology and method of administration).

Drug screening by urinary test should be performed at regular intervals.

PRECAUTIONS:

To be used with extreme caution in the following situations:

High-Risk Patients: Suicide attempts with opiates, especially in combination with tricyclic antidepressants, alcohol, and other CNS active agents, are part of the clinical pattern of addiction. Individualized evaluation and treatment planning, including hospitalisation, should be considered for patients who continue to exhibit uncontrolled drug use and persistent high-risk behaviour despite adequate pharmacotherapy.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. In view of ORLAAM's profile as a μ-agonist, it should be used with extreme caution and only if deemed essential in such patients.

Asthma and Other Respiratory Conditions: ORLAAM, as with other opioids, should be used with caution in patients with asthma, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Exacerbation of pre-existing asthma, skin rashes, and eosinophilia may be seen in patients predisposed to such atopic phenomenon (see section 4.3 regarding Contra-indications).

Special Risk Patients: Opioids should be given with caution and at reduced initial dose in certain patients, such as the elderly or debilitated, and those with prostatic hypertrophy, or urethral stricture. Patients with pre-existing diabetes mellitus or a pre-disposition to same may exhibit increases in serum glucose on ORLAAM. In patients with mild hepatic or mild renal impairment, the initial posology should be reduced and dose adjustment made with caution.

Acute Abdominal Conditions: As with other µ-agonists, treatment with ORLAAM may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Use in under 18 Years Old Addicts: The use of ORLAAM in addicts under 18 years of age has not been studied. Its use in this population should be carefully monitored by the treating physician.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed in humans**.**

Pharmacodynamic interactions between levacetylmethadol and potentially arrhythmogenic medicinal products. Concomitant treatment with the medicinal products mentioned in this section is contraindicated (see section 4.3 – Contra-indications):
- class I or III antiarrhythmics
- antihistamines that prolong QT interval (astemizole, terfenadine)
- antimalarials (chloroquine, halofantrine, quinine)
- calcium channel blockers (bepridil, lidoflazine, prenylamine, terodiline)
- neuroleptics that prolong QT interval (chlorpromazine, haloperidol, pimozide, sertindole, sultopride, thioridazine)
- antidepressants (amitriptyline, doxepin, imipramine, maprotiline)
- other medicinal products (cisapride, erythromycin IV, ketanserin, pentamidine IV, sparfloxacin, spiramycin)

Medicinal products known to induce hypokalaemia or hypomagnesaemia may also precipitate QT prolongation and thus interact with levacetylmethadol - These include:
- diuretics and laxatives
- supraphysiological use of steroid hormones with mineralocorticoid potential (e.g. systemic fludrocortisone).

These lists may not be exhaustive, and any medicinal product known to have the potential to prolong the QT interval should also not be used together with levacetylmethadol.

Polydrug and Alcohol Abusers - Patients who are known to abuse sedatives, tranquilizers, propoxyphene, antidepressants, benzodiazepines, and alcohol should be warned of the risk of serious overdose if these substances are taken while on ORLAAM maintenance.

Interaction with Narcotic Antagonists, Mixed Agonists/Antagonists, Partial Agonists, and Pure Agonists - As with other µ-agonists, patients maintained on ORLAAM may experience withdrawal symptoms when administered pure narcotic antagonists, mixed agonists/antagonists or partial agonists (see section 4.3 Contra-indications). Naloxone is contra-indicated in combination with ORLAAM, except for the treatment of overdosage. In addition, agonists such as meperidine and propoxyphene, which are N-demethylated to long-acting excitatory metabolites, should not be used by patients taking

ORLAAM because they would be ineffective unless given in such high doses that the risk of toxic effects of the metabolites becomes unacceptable.

Anesthesia and Analgesia - Patients receiving ORLAAM will develop a similar level of tolerance for opioids as patients receiving methadone. Anesthetists and other practitioners should be prepared to adjust their management of these patients accordingly.

Monoamine Oxidase Inhibitors - Coadministration may cause stimulation or depression of CNS (see section 4.3 Contra-indications).

The clinical effect of the combination of ORLAAM with a microsomal enzyme inducer/inhibitor is unpredictable regarding both the efficacy and safety of either product (see below).

Microsomal Enzyme Inducers - Rifampicin has been found to produce a marked (50%) reduction in serum methadone levels, leading to the appearance of symptoms of withdrawal in well stabilised methadone maintenance patients. Similar effects on serum methadone levels have been observed with carbamazepine, phenobarbital and phenytoin. Since ORLAAM is metabolized into a more active metabolite (nor-levacetylmethadol), administration of these drugs may increase ORLAAM's peak activity and/or shorten its duration of action.

Microsomal Enzyme Inhibitors - Erythromycin, cimetidine, anti-fungal drugs (ketoconazole or itraconazole), protease inhibitors (ritonavir, indinavir) and cyclosporin inhibit hepatic metabolism, may slow the onset, lower the activity, and/or increase the duration of action of ORLAAM. Caution and close observation of patients receiving these drugs are advised to allow early detection of any need to adjust the dose or dosing interval.

Safety and efficacy of ORLAAM with concomitant use of oral contraceptives have not been established. If use of ORLAAM is considered necessary, an alternative method of contraception (e.g. barrier method) should be used.

4.6 Pregnancy and lactation

(see sections 4.3 Contra-indications and 5.3 Preclinical safety data).

Use in Pregnancy - In the absence of sufficient data on the effects of ORLAAM in pregnant women and due to the embryotoxic effects observed in animal studies, its use is contra-indicated during pregnancy.

Labour and Delivery - The effects of ORLAAM on labour and delivery are not known. Like other μ-agonist opioids, however, ORLAAM is expected to produce respiratory depression and a possible neonatal dependence syndrome with a delayed emergence of withdrawal symptoms. Use of ORLAAM in labour and delivery is not recommended.

Nursing Mothers - The excretion of levacetylmethadol or its metabolites in human milk is unknown. Therefore, mothers on ORLAAM should not breast feed.

4.7 Effects on ability to drive and use machines

The use of ORLAAM may cause somnolence and euphoria. This may also occur when ORLAAM is taken with other compounds known to cause CNS depression or with alcohol. Patients should be warned not to engage in such activities.

4.8 Undesirable effects

Heroin or Methadone Withdrawal Reactions - Patients presenting for ORLAAM treatment are frequently in withdrawal from heroin or other opiates. They may display typical withdrawal symptoms, which should be differentiated from ORLAAM's side effects. Control of such symptoms is a primary goal of therapy. However, because of the slow onset and long half-lives of

levacetylmethadol, nor-levacetylmethadol and dinor-levacetylmethadol, overly aggressive increases in dosage to control these withdrawal symptoms with ORLAAM may result in overdose.

Signs and Symptoms of ORLAAM Excess - The interaction between the development and maintenance of opioid tolerance and ORLAAM dose can be complex. Dose reduction is recommended in cases where patients develop signs and symptoms of excessive ORLAAM effect, characterised by complaints of "feeling wired", poor concentration, drowsiness, and possibly dizziness on standing.

ORLAAM Withdrawal - Patients may experience withdrawal symptoms (nasal congestion, abdominal symptoms, diarrhoea, muscle aches, anxiety) over the 72-hour dosing interval if the dose of ORLAAM is too low. Physicians should be alert to the possible need for dose or dose schedule adjustments if patients complain of weekend withdrawal symptoms in the last day of the 72-hour dosing interval.

The following adverse events were observed:

Incidence greater than 1%

Body as a Whole	Asthenia, back pain, chills, edema, hot flushes, flu syndrome and malaise, pharmacodependence.
Gastrointestinal	Abdominal pain, constipation, diarrhoea, dry mouth, nausea and vomiting.
Musculoskeletal	Arthralgia.
Nervous System	Abnormal dreams, anxiety, decreased sex drive, depression, euphoria, headache, hypesthesia, insomnia, nervousness, somnolence.
Respiratory	Cough, rhinitis, and yawning.
Skin/appendages	Rash, sweating.
Special senses	Blurred vision.
Urogenital	Difficult ejaculation, impotence.

Incidence less than 1%

Cardiovascular	Postural hypotension, prolongation of the QT interval resulting in some cases in severe arrhythmias (torsade de pointes), non-specific ST-T wave changes.
Musculoskeletal	Myalgia.
Special senses	Lacrimation.
Hepatic	Hepatitis and abnormal liver function tests.
Urogenital	Amenorrhea, pyuria.

4.9 Overdose

Signs and Symptoms: All cases of ORLAAM overdose have involved multiple drugs. Overdose on ORLAAM alone has always been the result of too frequent (daily) dosing or inadvertent overdosing. Overdose is primarily of concern in persons not tolerant to opiates, since in such individuals a dose of 20 to 40 mg of ORLAAM may cause somnolence, and a larger initial dose may cause serious overdose. Tolerant individuals will generally not show symptoms unless higher doses are administered.

In ORLAAM overdose, as with other μ-agonist opioids, the following signs and symptoms should be anticipated: respiratory depression, extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin, bradycardia, and hypotension. In severe overdose, apnea, circulatory collapse, pulmonary edema, cardiac arrest and death may occur.

Treatment: In the case of ORLAAM overdose, protect the patient's airway and support ventilation and circulation. Absorption of ORLAAM from the gastrointestinal tract may be decreased by gastric emptying and/or administration of sodium sulphate as a laxative together with activated charcoal.

(Safeguard the patient's airway when employing gastric emptying or administering charcoal in any patient with diminished consciousness). Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion are unlikely to be beneficial for ORLAAM overdose due to its high lipid solubility and large volume of distribution.

In managing ORLAAM overdose, the physician should consider the possibility of multiple drugs, the interaction between drugs, and any unusual drug kinetics in the patient. Naloxone may be given to antagonize opiate effects, but the airway must be secured as vomiting may ensue. If possible, naloxone should be titrated to clinical effect rather than given as a large single bolus, since rapid reversal of opioid effects by large naloxone doses can cause severe precipitated withdrawal effects that may include cardiac instability. If a patient has received a total of 10 mg of naloxone without clinical response, the diagnosis of opioid overdose is unlikely.

If the patient does respond to naloxone, the physician should remember that the duration of ORLAAM activity is much longer (days) than that of naloxone (minutes) and repeated dosing with or continuous intravenous infusion of naloxone is likely to be required. Use of oral naltrexone in this setting is not recommended because it may precipitate prolonged opioid withdrawal symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid Analgesic, ATC code: NO2AC.

Levacetylmethadol is a synthetic opioid agonist with actions qualitatively similar to morphine (a prototypic μ-agonist). Tolerance to these effects develops with repeated use.

Levacetylmethadol exerts its clinical effects in the treatment of opiate abuse through two mechanisms. First, ORLAAM cross-substitutes for opiates of the morphine-type, suppressing symptoms of withdrawal in opiate-dependent individuals. Second, chronic oral administration of ORLAAM can produce sufficient tolerance to block the subjective “high” of usual doses of parenterally administered opiates.

The duration of action of a single dose of ORLAAM is due to the sum of the opioid activity of the parent drug and its metabolites. A single dose of orally administered ORLAAM has an onset of opioid effects averaging 2 to 4 hours after ingestion and a duration of action of 48 to 72 hours (as measured by pupillary constriction and suppression of abstinence signs). Single oral doses of 30 to 60 mg of ORLAAM eliminate signs of abstinence for 24 to 48 hours in individuals maintained on high doses of morphine who are abruptly withdrawn. At higher doses (80 mg and above), suppression of withdrawal can increase to 48 to 72 hours in most individuals.

Chronic oral administration of 70 to 100 mg of ORLAAM three times weekly produces tolerance which blocks the “high” of a 25 mg dose of intravenously administered heroin for up to 72 hours; maintenance on lower doses (50 mg) of ORLAAM produces only partial blockage for the same period.

5.2 Pharmacokinetic properties

Absorption:

Levacetylmethadol is rapidly absorbed from an oral solution. Plasma levels are detectable within 15 to 30 minutes after ingestion and reach their peak within 1.5 to 2 hours at steady-state.

Metabolism and Elimination:

Levacetylmethadol undergoes first-pass metabolism to its demethylated metabolite nor-

levacetylmethadol, which is sequentially N-demethylated to dinor-levacetylmethadol. Both metabolites are active and contribute to the extent and duration of ORLAAM's clinical activity. While N-demethylation by CYP 3A4 is the primary route of metabolism, minor pathways of elimination include direct excretion and deacetylation to methadol, nor-methadol, and dinor-methadol.

Special Populations:

Elderly - No pharmacokinetic data in elderly patients are available.

Gender - Males showed a trend toward a slower conversion of levacetylmethadol to nor-levacetylmethadol, which may alter the plasma concentration profile of ORLAAM and its active opioid metabolites. Physicians should be alert to a possible gender difference.

Hepatic and Renal Disease - At the present time no pharmacokinetics studies have been carried out in subjects with clinically significant hepatic insufficiency or renal impairment. Both the pharmacokinetics and pharmacodynamics of opiate agonists may be altered in these subjects.

5.3 Preclinical safety data

Levacetylmethadol has not been adequately tested for genotoxic potential. In some studies there was evidence of a genotoxic effect**.**

Levacetylmethadol caused uterine and thyroid tumors and leukemia in long term rodent studies. The clinical relevance of these findings is not known**.**

Administration of levacetylmethadol did not result in teratogenic effects in animals but was embryotoxic. In utero or lactational exposure to levacetylmethadol led to a decreased rat pup viability, survival and growth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methylparaben, propylparaben, hydrochloric acid and purified water.

6.2 Incompatibilities

None identified.

6.3 Shelf-life

- Shelf-life of the product as packaged for sale: two years
- Shelf-life after dilution according to directions: to be used within 48 hours
- Shelf-life after first opening the container: 6 months.

6.4 Special precautions for storage

Store at controlled room temperature (15-25°C), protect from direct sunlight.

6.5 Nature and contents of container

ORLAAM Oral Solution (10 mg/ml) is a clear, colourless liquid supplied in 120 ml and 500 ml plastic bottles.

6.6 Instructions for use and handling, and disposal (if appropriate)

Since ORLAAM is classified as a narcotic, appropriate security measures should be taken to safeguard stock of ORLAAM and care should be taken for the safe disposal of the product.

ORLAAM is diluted before administration and should be mixed with slightly acid diluent (such as fruit juice or carbonated soft drink) immediately prior to dispensing. The diluted solution is stable for up to 48 hours at room temperature. The bottle should be discarded 6 months after opening.

ORLAAM is compatible with the materials used in most dispensing systems.

7. MARKETING AUTHORISATION HOLDER

SIPACO INTERNACIONAL, Lda.
Avenida 5 de Outubro, 267 – 6° dto
1600 LISBON
PORTUGAL

8. NUMBERS IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/97/041/001
EU/1/97/041/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/07/97
16/03/98

10. DATE OF REVISION OF THE TEXT

PACKAGE LEAFLET

1. NAME OF THE MEDICINAL PRODUCT

ORLAAM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance : Levacetylmethadol hydrochloride, 10 mg / ml.
Excipients : Methylparaben, propylparaben, hydrochloric acid and purified water.

3. PHARMACEUTICAL FORM AND CONTENTS

Oral solution. Bottle of 120 ml and 500 ml.

4. PHARMACOTHERAPEUTIC GROUP

Opiate analgesic.

5. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORIZATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Sipaco Internacional Lda., Av. 5 de Outubro 267 – 6° dto, 1600 Lisbon, Portugal

6. THERAPEUTIC INDICATIONS

This product is exclusively reserved for the substitution maintenance treatment of opiate pharmacodependence following treatment with methadone, as part of comprehensive treatment plan, including medical, social and psychological care, based on an agreement between the patient and his/her physician.

7. INFORMATION NECESSARY BEFORE TAKING THE MEDICINAL PRODUCT

ORLAAM is not intended for take home use. It should be administered under the supervision of your physician and whenever practicable, in specialised treatment centers.

This medication MUST NOT BE USED in the following cases:

- hypersensitivity to ORLAAM
- moderate to severe respiratory impairment
- children under 15 years
- breast feeding
- pregnancy
- moderate to severe renal impairment
- moderate to severe hepatic impairment
- treatment with narcotic antagonists or agonists / antagonists (except for the treatment of overdosage)
- treatment with certain antidepressants
- patients with known or suspected ECG abnormality (QT prolongation) such as congenital or acquired long QT syndrome or conditions which may lead to QT prolongation:
  - a slow heartbeat,
  - significant heart disease,

- patients being treated with other medicinal products to control the heart rhythm, or with other medicinal products known to induce ECG abnormality (QT prolongation) (see Interaction with other medicaments and other interactions),
- patients having low blood salts (especially low potassium or low magnesium), being treated with medicinal products known to lower blood salts or having a medical condition that could result in low blood salts (loss of appetite, vomiting and diarrhoea).

IN CASE OF DOUBT, IT IS ABSOLUTELY NECESSARY TO ASK ADVICE FROM YOUR PHYSICIAN OR YOUR PHARMACIST.

Special warnings:

- Administration of this product on a daily basis is hazardous due to excessive drug accumulation and risk of fatal overdose.
- The peak activity of this product is not immediate. The use or abuse of other psychoactive substances, including alcohol, may result in fatal overdose, specially with the first few doses of ORLAAM, either during initiation of treatment or after a lapse in treatment.
- This product may induce a pharmaco-dependence.
- ORLAAM may make the heart beat irregularly causing you to feel dizzy or have palpitations, feel faint or have convulsions. If it appears **you must seek urgent medical advice**.

Use this medication WITH CAUTION in certain diseases:
- asthma and other chronic lung diseases
- pre-existing allergic conditions
- liver disease
- kidney disease
- underactive thyroid
- Addison's disease
- enlarged prostate or problems with urination
- diabetes mellitus

IN CASE OF DOUBT, DON'T HESITATE TO ASK ADVISE FROM YOUR PHYSICIAN OR YOUR PHARMACIST.

Interaction with other medicaments and other interactions:

- The following medicinal products may induce ECG modifications (QT prolongation) and therefore must never be taken during the course of Orlaam treatment (see section This medication MUST NOT BE USED in the following cases):

    - others medicinal products to control the heart rhythm
    - medicinal products for the treatment of angina, high blood pressure or an irregular heart beat (calcium channel blockers: bepridil, lidoflazine, prenylamine, terodiline),
    - medicinal products for allergies or hay fever (antihistamines: astemizole, terfenadine)
    - certain medicinal products for the treatment of mental conditions: certain neuroleptics (chlorpromazine, haloperidol, pimozide, sertindole, sultopride, thioridazine) or certain antidepressants (amitriptyline, doxepin, imipramine, maprotiline),
    - antimalarials (chloroquine, halofantrine, quinine)
    - other medicinal products (cisapride, erythromycine IV, ketanserin, pentamidine IV, sparfloxacin, spiramycin).

- Medicinal products known to induce low blood salts (especially low potassium or low magnesium) must also never be taken during the course of ORLAAM treatment: diuretics, laxatives or high doses of steroid hormones (fludrocortisone).

- Use of ORLAAM with sedatives, tranquilizers, propoxyphene and antidepressants may increase the risk of overdose and requires close medical monitoring.

IN ORDER TO PREVENT POTENTIAL INTERACTIONS BETWEEN SEVERAL MEDICATIONS, YOUR PHYSICIAN OR YOUR PHARMACIST MUST BE NOTIFIED OF ANY OTHER ONGOING OR RECENT TREATMENT.

You should not take any other opiates or narcotics while on ORLAAM. This might result in serious overdose:

- Consumption of alcoholic beverages and medications containing alcohol must be avoided.
- The efficacy of oral contraceptives might be reduced by ORLAAM. The use of another contraceptive method (e.g. barrier method) is recommended.

Pregnancy and lactation:

The use of this product is contra-indicated during pregnancy.

Mothers on ORLAAM should not breast feed.

Drivers and machine operators:

Administration of ORLAAM may cause drowsiness or euphoria. This could be increased by alcohol or other medicines. If your alertness or behaviour are affected by this product, avoid engaging in such activities.

8. INSTRUCTIONS FOR PROPER USE

Dosage:

Doses of ORLAAM are individualised and are adjusted progressively under medical surveillance according to the needs of the patient.
STRICTLY FOLLOW THE PRESCRIPTION OF YOUR PHYSICIAN.
Effectiveness of this product depends on:

- the posology
- the associated medical, social, psychological and rehabilitative care

Administration:

THIS PRODUCT IS DILUTED IMMEDIATELY PRIOR TO DISPENSING FOR ORAL ADMINISTRATION AND SHOULD BE MIXED WITH SLIGHTLY ACIDIC DILUENTS SUCH AS FRUIT JUICE OR CARBONATED SOFT DRINKS.

Frequency and timing of administration:

This medication must be administered in one dose, every-other-day or three times a week, as determined by the prescriber. Do not take a daily dose.
STRICTLY FOLLOW THE PRESCRIPTION OF YOUR PHYSICIAN.

Action to be taken if one or more doses have been omitted:

If you miss one or more scheduled doses of this product, or have deviated from your prescription, notify your physician immediately as treatment may need to be adjusted.

Duration of treatment:

Duration of the treatment with this product must be determined for each individual patient. The decision to modify, reduce, or discontinue therapy with this product must be made as part of a comprehensive treatment plan by your physician and with your agreement.
STRICTLY FOLLOW THE PRESCRIPTION OF YOUR PHYSICIAN.

Action to be taken in case of overdose:

Overdosage with ORLAAM requires medical surveillance of the patient and possibly emergency treatment in the hospital.

Risk of withdrawal syndrome:

A withdrawal syndrome may develop upon abrupt interruption of treatment.

9. DESCRIPTION OF UNDESIRABLE EFFECTS UNDER NORMAL USE

During treatment, the following have been observed:
- asthenia, back pain, chills, edema, hot flushes, flu syndrome and malaise, pharmacodependence
- abdominal pain, constipation, diarrhoea, dry mouth, nausea and vomiting
- joint pain
- abnormal dreams, nervousness or restlessness, decreased sex drive, depression, feeling “high”, headache, decreased sensitivity to touch, insomnia, drowsiness
- cough, nasal congestion and yawning
- rash, sweating
- blurred vision
- difficult ejaculation, impotence

More rarely:
- low blood pressure
- muscle aches
- tearing
- ECG abnormalities, rhythm disturbances of the heart.

NOTIFY YOUR PHYSICIAN OR YOUR PHARMACIST WITH ANY UNDESIRED EFFECT NOT MENTIONED ABOVE.

10. STORAGE CONDITIONS

- The expiry date is printed on the label. Do not use the product after this date.
- The product must be used within 48 hours after dilution.
- The product must be stored at room temperature, protected from direct sunlight.
- Shelf-life after first opening the container: 6 months.
- Appropriate care should be taken for the safe disposal of the product.

11. DATE OF LAST REVISION