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

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EMEA PUBLIC STATEMENT ON THE RECOMMENDATION TO SUSPEND THE MARKETING AUTHORISATION FOR ORLAAM (LEVACETYLMETHADOL) IN THE EUROPEAN UNION

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[1]. 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.

In December 2000, following 10 cases of life-threatening cardiac disorders including ventricular rhythm disorders such as Torsade de pointes reported in patients treated with Orlaam (levacethylmethadol), the European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP), had decided, as an interim and precautionary measure while performing a full comparative risk/benefit re-assessment of Orlaam, to advise prescribers not to introduce any new patients to Orlaam therapy.

Following the re-assessment of the risk and benefit balance of Orlaam in comparison to the existing alternatives, the potential of Orlaam to significantly increase the QTc interval and to be proarrythmic has been consistently shown based on the electrophysiological and clinical studies and reports from the spontaneous system. Moreover, based on the absence of supporting data, it was not possible to identify any "niche" indication where the therapeutic benefit would outweigh the occurrence of severe, serious and unpredictable cardiotoxicity associated with the use of Orlaam.

The CPMP of the European Medicines Evaluation Agency (EMEA), during its meeting of 26-28 March 2001, adopted an Opinion recommending by consensus the suspension of the marketing authorisation of Orlaam. The background to this procedure and the grounds for the suspension are annexed to this Public Statement.

In view of the decision made by its scientific committee, the EMEA wishes to draw attention to the following:

- **Physicians who are currently treating patients with Orlaam are advised to review their patients immediately. In addition, physicians are advised to switch their patients from Orlaam to another existing alternative, e.g. 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.

- **Alternatively, if the physician decides to detoxify his patient from Orlaam:**

  The decision to detoxify patients from Orlaam should be made on an individual basis; both gradual reduction (5 to 10% a week) and abrupt withdrawal schedules have been

[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. 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.

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used successfully. 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.

- **Patients being treated with Orlaam should contact their prescribers without delay, they must not stop Orlaam suddenly without seeking medical advice.**

Existing supplies of Orlaam will be progressively withdrawn from pharmacies in order to allow the switch of patients from Orlaam to other existing therapeutic alternatives. The EMEA thought it necessary to provide this new information to the public.

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Background and Grounds for Opinion Suspending the Marketing Authorisations of ORLAAM

1. Comparative safety profile of levacethylmethadol as compared to existing therapeutic alternatives

- *Safety profile of levacethylmethadol*

Ten cases of severe cardiac rhythm disorders were reported to the MAH since July 1997 (see also Table annexed). They included 3 cases of cardiac arrhythmia, 3 cases of cardiac arrest associated with ventricular arrhythmias. The QT interval was prolonged in 7 of the patients (from 525 msec to 800 msec) and 7 of these patients had an episode of Torsade de pointes. Three patients required a pacemaker insertion. In three cases, there was a dose in excess of the SPC recommendations, and in one case concomitant administration of methadone. One case occurred while under treatment with anti-HIV drugs. At least two patients were switched back to methadone without recurrence of the cardiac event. Four other asymptomatic cases of prolongation of the QT interval were also detected by routine screening ECGs. Other serious and non-serious ADRs reported from either clinical trials or post-marketing experience include signs of overdose (apnoea, respiratory depression, somnolence). Constipation is the most frequently reported ADR.

As it was demonstrated in the past for several other medicinal products, the predictive value of a monitoring (in that particular case, an ECG) in order to prevent the occurrence of these life-threatening cardiac disorders is quite poor. If such a monitoring is put in place it should be performed frequently during the first 2-4 weeks of treatment with Orlaam, as the effect on QTc interval was shown to be evident within 2 weeks of Orlaam treatment in most patients. The ECG records should be analysed by a cardiologist for evidence of a QT interval prolongation. Values of QTc interval of 500 msec or more or an increase in QTc interval > 60 msec from baseline in an individual is predictive of proarrhythmic risk.

Clinical studies where the QTc interval was systematically measured showed a significant increase in QTc interval when the patient was switched from methadone to ORLAAM, demonstrating the greater proarrhythmic potency of LAAM compared to methadone. In a more recent study (ORL0495), preliminary analyses showed that in 8/58 cases the difference of the QTc interval between Orlaam and baseline was >60 msec. The comparison to methadone for these cases showed a difference ranging from 7 to 82 msec, with a mean (s.d.) of 34.5 msec (24.7) and a median of 31 msec. The absolute QTc value was >450 msec in 4 cases, ranging from 451 to 471 msec.

These case reports were supported by electrophysiological data showing that levacetylmethadol is highly proarrhythmic. Preclinical studies in dogs have shown significant ECG changes. A recent electrophysiological study using Purkinje fibres and ventricular myocytes has confirmed that the parent drug and its metabolites both prolong the APD_{90}, with a larger effect by the parent drug LAAM than by its two metabolites. The effect is concentration-dependent. Levacetylmethadol was also found to block the rapid component of delayed rectifier potassium current (IKr). LAAM and its metabolite, dinor-LAAM, are more potent blockers of IKr than are nor-LAAM or methadone. LAAM is also a sodium channel blocker while its metabolites are not. A combination of class I and class III activities is highly proarrhythmic.

- *Safety profile of therapeutic alternatives available in the EU: methadone and buprenorphine*

Electrophysiological data suggest that, like Orlaam, methadone is associated with the potential to prolong the QTc interval.

This potential has been further studied in a clinical study where the effect of methadone on ECG was compared to values obtained at baseline. Preliminary results can currently be analysed only qualitatively but confirm results of the electrophysiological study. An exploratory observational study also suggested that methadone is associated with a prolongation on the QTc interval in users of psychoactive drugs.

Some cases of clinically significant cardiac events (incl. cases of Torsade de pointes) were reported in the United-States and in France in patients treated with high doses of methadone for chronic pain. Although the level of undereporting is probably high, and given the probably very large number of patients exposed to methadone in the US for pain relief, the reporting rate of severe cardiac arrhythmia

associated with methadone appears to be much lower than for Orlaam. These clinical data are consistent with electrophysiological findings: methadone has a potential for prolongation the QT interval and being proarrhythmic, especially at high doses, but this potential is much lower than for Orlaam. From the data available, the QT prolonging potential of methadone does not appear to have clinical consequences at doses normally used in maintenance treatment programmes. It is noteworthy that in at least two cases of cardiac events having occurred with Orlaam, switching back to methadone did not induce recurrence of these events.

High dosage buprenorphine has been marketed in several European countries since 1996 in the treatment of major pharmacodependence to opioids with concomitant medical counselling. The largest experience in this indication comes from France.

Concerning buprenorphine, the reporting rate of cases of death is stable since 1996 and might be estimated to be between 1/2000 and 1/1500 patients treated with buprenorphine. From these cases, it was concluded that most of the reported deaths are linked to product misuse situations. Respiratory depression is the most likely hypothesis to explain the occurrence of these deaths and the risk of respiratory depression probably increases with the dose of buprenorphine and "off-label" IV use. Benzodiazepines and other psychoactive drugs probably potentiated the onset of respiratory depression. One study demonstrated that the mortality associated with buprenorphine was inferior to the mortality among the patients treated with methadone. In addition, in 13 studies in which Orlaam and methadone have been compared, mortality was 0.8% among 3495 patients treated with Orlaam and 0.4% among 1648 patients treated with methadone. The mortality associated with injected illicit opiates has been estimated as high as 1.8% (1 in 56) par year.

In conclusion, the CPMP concluded that electrophysiological studies, clinical studies and reports from the spontaneous system provide consistent evidence that Orlaam has the potential to significantly increase the QTc interval and to be proarrhythmic. There was no indication that lowering the maximum recommended dose of Orlaam would reduce its cardiotoxicity, because several clinical cases of cardiac arrhythmia occurred at the average recommended dose. Moreover, there is a very large inter-patient variability in the rate of metabolisation from the parent drug to its metabolites. This variability could also vary in time with use of concomitant medications. Accumulation of LAAM could occur even at a normal dosage. Since the parent drug is largely responsible for cardiotoxicity and the metabolites for therapeutic effect, there are significant risks from administration of inhibitor of CYP 3A4 - the isoform responsible for metabolism of LAAM - and from the presence of liver disease.

Consequently, the claimed advantage of Orlaam, a thrice-weekly administration, cannot justify anymore on its own a switch from methadone to Orlaam.

2. Therapeutic efficacy of levacethylmethadol as compared to existing therapeutic alternatives

In a second step, the CPMP tried to find a niche indication for Orlaam. The main advantage of Orlaam was its pharmacokinetic behaviour leading to a longer pharmacodynamic action in comparison to methadone. This offered the advantage of three times weekly administration as compared to the daily administration of methadone. On other clinically relevant endpoints the efficacy of Orlaam is similar to that of methadone, but more patients leave the studies because of withdrawal symptoms during the induction phase. There is a trend towards less illicit drug use in the Orlaam users than in the methadone users, based on urine testing. The CPMP considered that the possible therapeutic benefits of levacethylmethadol as compared to the existing therapeutic alternatives may be as follows:

1 - In patients needing high doses of methadone due to a high clearance. In that case an increase of methadone dose to high levels is necessary. Up to 10% of the patients may need high dose of methadone, partially due to extensive metabolism. In routine practice it is practically impossible to identify those patients with a high CYP 3A4 activity. The identification of these patients is based primarily on clinical end-points. . When such situation occurs, two options may be considered for these patients:

- An increase of the daily dose of methadone at a higher level than the standard posology (i.e. daily doses higher than 60 to 100 mg).
- The use of a therapeutic alternative. Orlaam could be considered as a possible therapeutic alternative only for those patients who may be in a situation of clinical failure with their treatment with methadone used at appropriate doses or in those patients who experienced some disabling/serious side effects with methadone. In addition, Orlaam could perhaps be restricted to those patients in whom, due to interactions or individual characteristics, methadone dosage leads to sub-therapeutic plasma levels and repeated doses are needed. However, one cannot predict that such rapid metabolisers of CYP 3A4 would still be adequately protected against the cardiotoxic effect of Orlaam. Actually the ratio of concentrations of metabolites/LAAM is highly variable. In some patients, the metabolites could accumulate due to extensive metabolism and produce their own cardiotoxic effect. Finally, such rapid metabolisers would be difficult to identify in the routine practise. Consequently, the argument of safety to justify the use of Orlaam in CYP 3A4 rapid metabolisers was only hypothetical and needed to be adequately substantiated. The CPMP recognised that no data are currently available in order to support these restriction of indication.

2 - Patients with an extensive metabolism phenotype may require more than one daily dose of methadone. In this case due to the shorter half-life of methadone a splitting of the daily dose could be necessary. The use of Orlaam in these patients might lead to an increase of the levels of the two active metabolites of levacethylmethadol (nor-LAAM or dinor-LAAM). There are indications in the electrophysiological trials that these metabolites are less cardiotoxic than the mother compound. The clinical consequences are unpredictable. Without data, such effects cannot be reliably predicted.

3. Conclusions and risk/benefit assessment

In conclusion, electrophysiological studies, clinical studies and reports from the spontaneous system provide consistent evidence that Orlaam has the potential to significantly increase the QTc interval and to be pro-arrhythmic. Moreover, this potential is greater than that observed with methadone. The therapeutic efficacy for Orlaam does not outweigh the risk of severe and potentially fatal ventricular arrhythmias. In light of the data establishing these risks and the consequent negative risk-benefit balance, the CPMP concluded that Orlaam is proven to be harmful in normal conditions of use.

The CPMP considered that levacethylmethadol could be a possible therapeutic alternative in patients with therapeutic failure on methadone. It was noted by the CPMP, however, that clinical data to support even such a restricted indication were currently lacking.

The CPMP has therefore recommended the suspension of the marketing authorisation for Orlaam.