EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for VIMPAT

International Non-proprietary Name: **lacosamide**

Procedure number: EMEA/H/C/863/A-20/0026

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Vimpat (lacosamide) was authorised through the centralised procedure on 29 August 2008. It is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. It is available as film-coated tablets (50, 100, 150 and 200 mg), syrup (15 mg/ml) and solution for injection (10 mg/ml).

Regarding the 15 mg/ml syrup formulation, a quality defect was reported, which concerned the formation of a precipitate in the product.

The appearance of a precipitate in Vimpat syrup was first reported to the European Medicines Agency (EMA) in October 2010 and concerned a pharmacy complaint for a precipitate in one bottle of Vimpat syrup. This specific batch of syrup was recalled. The Marketing Authorisation Holder (MAH) carried out a root cause analysis to investigate the reasons for the formation of the precipitate. In April 2011 the MAH provided a report to the EMA which showed that the precipitate was positively identified as lacosamide, i.e. the active substance of the product. It was also believed that the occurrence of the precipitate was confined to one single batch, since no retained samples exhibited any precipitation, except the batch which concerned the October 2010 complaint and which had been recalled.

This particular batch had been manufactured slightly differently than normal (compounding mixing time shorter than usual) which was thought to have led to non-complete dissolution of lacosamide. Further solubility studies were carried out which showed that the solubility of lacosamide in the syrup matrix actually is lower than 15 mg/ml, and the syrup formulation was thus supersaturated with respect to lacosamide. The MAH committed to study the precipitation phenomenon further.

On 17 June 2011 a new report was provided to the EMA by the company. Additional complaints regarding precipitates in the Vimpat syrup had been reported by pharmacies. This time, the retained samples of the syrup showed precipitation in 16 out of 21 batches. In the 17 June report, there was indication that even if the syrup was affected by precipitation, the liquid phase still appeared to contain lacosamide within specification and its content seemed to be homogeneous within the bottle (analysis performed on one bottle from one batch only though). The company suggested that the way to go forward would be on the long term to replace the Vimpat 15 mg/ml syrup with the 10 mg/ml syrup (a product which is currently approved in the US). On the short term the company proposed, on a medical rationale, to continue supply patients who couldn't be switched to tablets with the syrup formulation. This proposal was discussed at the June CHMP and a list of eight questions was sent to the MAH to be addressed by 30 June 2011.

The analysis of additional Vimpat syrup bottles showed that there was a substantial risk that lacosamide was not evenly distributed in the bottles which might lead to either under or over dosing. It was also communicated by the MAH that no technical remediation was possible at that stage. The 30 of June response was followed by a communication from the company to the EMA on 1 July with a proposal to undertake a voluntary Class II recall for Vimpat 15 mg/ml syrup from the EEC market. The MAH also presented a recall and communication plan, as well as Direct Healthcare Professional Communications (DHPCs) to inform physicians, pharmacists, prescribing nurses (UK), wholesalers and patient advocacy groups of the precipitation defect of the product. In addition, the timeframe of transitioning patients to an alternative treatment was proposed by the company and how to adequately encompass tapering off the lacosamide treatment for the patients using the syrup.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 8 July 2011 to assess the above concerns and its impact on the benefit/risk balance for Vimpat syrup 15mg/ml, and to give its opinion on measures necessary to ensure the safe and effective use of Vimpat syrup 15mg/ml, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

After reviewing all the available data submitted by the MAH to address the concerns discussed, the CHMP adopted an opinion on 22 September 2011.

2. Scientific discussion

2.1. Quality aspects

Based on the data provided by the MAH, at the time of the initial marketing authorisation application, lacosamide syrup formulations with Active Product Ingredient (API) concentrations of 10, 15, 20 and 25 mg/ml were produced within the frame of the kinetic experiments performed. After solubilization of the API at 55°C, precipitation after cooling to room temperature was observed for the 20 and 25 mg/ml formulations whereas the 10 and 15 mg/ml formulations remained clear. Subsequent stress stability studies at 40°C (3 weeks), at 2-8°C (3 days) and freeze thaw studies (-20°C) showed that the 10 and 15 mg/ml remained unchanged. Consequently, the maximum concentration of API in lacosamide syrup was initially defined as 15 mg/ml.

Following the quality complaints received by the pharmacies, results of additional thermodynamic experiments were submitted to CHMP in June 2011. These demonstrated that the thermodynamic solubility of lacosamide in Vimpat 15 mg/ml syrup is in the 13.6-13.8 mg/ml range at 20°C and hence is below the 15 mg/ml concentration of the commercial formulation. This means that the 15 mg/ml formulation is slightly supersaturated in terms of lacosamide concentration. From a thermodynamic point of view, as the 15 mg/ml syrup is in a non-equilibrium metastable state, initiation of irreversible precipitation is likely to occur whenever the activation energy for precipitation is overcome. The presence of a lacosamide seed or a minor nucleation on the glass bottle wall can initiate the precipitation. As it is driven by kinetics, the occurrence of the precipitation cannot be predicted.

The MAH was also asked which measures could be implemented in order to prevent crystallisation. In that respect, the company investigated thermodynamic lacosamide solubility at different temperatures by measuring the lacosamide solubility at different temperature in a 15 mg/ml matrix formulation (containing one and two paraben). The results are presented in the Table below. The results as presented by the MAH suggest that lacosamide solubility depends on the storage temperature, with a higher solubility observed at a higher storage temperature (55°C), resulting in a more thermodynamic stable syrup formulation. On the other hand, a low storage temperature (5°C) renders the lacosamide syrup more viscous, thereby limiting the diffusion rate of lacosamide molecules towards a nucleation point or precipitate surface. These two parameters, solubility and viscosity, are in counterbalance at various storage temperatures. Currently, data on precipitate growth rate as a function of temperature are not available. Therefore, the company indicated that changing storage conditions may not be sufficient to prevent the occurrence or progression of flake-like precipitate in the Vimpat 15 mg/ml syrup.

Table :1 Lacosamide Thermodynamic solubility at different storage temperature

Analytical references	Batches	Temperature	Results (mg/ml)
			Lacosamide
03-RO-0101-13	Two paraben formulation	5°C	9.6
03-RO-0101-14	Single paraben formulation	5°C	9.0
03-RO-0101-16	Two paraben formulation	20°C	13.6
03-RO-0101-17	Single paraben formulation	20°C	13.8
03-RO-0112-4	Two paraben formulation	55°C	> 24.0
03-RO-0112-8	Single paraben formulation	55°C	> 24.0

Conclusions on Quality

The appearance of the lacosamide precipitation in the Vimpat 15 mg/ml syrup was considered by the CHMP a serious quality defect. The reason for the precipitation is the fact that the formulation is supersaturated with respect to lacosamide. Recent studies suggest a saturated solubility of about 13.7 mg/ml lacosamide in the syrup matrix at 20°C and that the 15mg/ml syrup is in a non-equilibrium metastable state. Precipitation has not been observed upon release of the product but it occurs with time in an unpredictable way.

The experiments carried out by the MAH regarding the solubility characteristics of lacosamide in the syrup matrix at different temperatures demonstrate that changing the temperature storage conditions for the 15 mg/ml syrup to avoid the problem of lacosamide precipitation is not an appropriate way forward.

The results from limited studies on homogeneity after shaking are inconclusive. Previously submitted studies where bottles of Vimpat syrup 15mg/ml with precipitation were shaken for 10 seconds or 20 seconds showed that these mixing times were inadequate to provide a homogeneous solution. In general, shaking of bottles of Vimpat 15mg/ml syrup for 30 seconds improved the homogeneity; however, non-homogeneity could still be observed. Therefore, it could not be concluded that it would be beneficial to recommend to patients to shake the bottle before use.

Since no technical remediation was foreseen, the MAH is voluntarily recalling the Vimpat 15 mg/ml syrup from the market as of 15 September 2011. During the July 2011 meeting the CHMP noted the intention of the MAH to submit an application for a 10 mg/ml syrup as a substitute for the 15 mg/ml syrup.

2.2. Clinical aspects

It has been observed in the affected bottles of product that lacosamide may be unevenly distributed within the bottle, thus leading to potential under or overdosing for the patient. An underdosing could result in seizures with potentially serious consequences for the patient and an overdosing could increase the adverse event rates.

The risk for patients continuing on the Vimpat syrup 15mg/ml with the possibility of dose fluctuations is therefore higher than the risk of an elective and controlled switch to another pharmaceutical form of lacosamide or to another anti-epileptic drug.

In case that a switch to another anti-epileptic treatment is decided it was recommended to be done gradually in accordance with the current clinical practice (i.e. taper the daily dose by 200 mg every week). Some patients not able to swallow tablets would from a clinical perspective clearly benefit from continuing with Vimpat syrup. The MAH has currently licensed in the USA an oral solution with a different strength (i.e. 10mg/ml). The CHMP noted the intention of the company to make this product available via national systems for prescription on a named patient basis.

2.3. Risk minimisation activities

The CHMP did not ask the MAH to submit a Risk Management Plan.

2.4. Product information

The Product Information (PI) for Vimpat has been amended to delete the syrup formulation and any relevant cross-reference to the syrup in the PI of the remaining formulations.

3. Overall discussion and benefit/risk assessment

The appearance of the lacosamide precipitation in the Vimpat 15 mg/ml syrup caused by supersaturation of the syrup was considered a serious quality defect.

Analyses also suggested that the lacosamide concentration is not homogeneously distributed in the syrup due to sedimentation of the crystals of lacosamide at the bottom of the bottle and this may have an impact on the dose administered. Crystallisation has not been observed upon release of the product but it occurs over a period of time in an unpredictable way.

There is no possible technical remediation and due to the non-homogeneity of the concentration of lacosamide in the bottle, this could result in either under or overdosing. A lower exposure than

intended could result in seizures with potentially serious consequences for the patient and a higher exposure could increase the adverse event rates.

Taken this into account, the benefit/risk balance for Vimpat syrup 15mg/ml is considered no longer positive under normal conditions of use.

4. Overall conclusion

Having considered the overall submitted data provided by the MAH in writing, the CHMP concludes that the risk-benefit balance is not positive for Vimpat syrup 15mg/ml under normal conditions of use.

Therefore, the CHMP recommends the variation of the marketing authorisation of Vimpat to delete the syrup formulation from the Marketing Authorisation.

The revised summary of product characteristics, labelling and package leaflet are set out respectively in annexes I, IIIA and IIIB of the opinion.

5. Action plan

During the July 2011 CHMP meeting, the CHMP agreed on a communication plan and on the wording of a 'Dear Healthcare Professional Communication' (DHCP).

The letter was designed to inform prescribers of the recall and the recall date, of the precipitation defect, the root cause and the effects on the administered dose. It was also stated that no new patients should be initiated on Vimpat syrup providing alternative therapeutic solutions as well as guidelines to ensure a smooth switch until the recall takes place (see attachment 4 to this Report).

The Marketing Authorisation Holder released the DHPC letter on 28 July 2011 informing of an actual recall of Vimpat syrup from the market due on 15 September 2011.

Similar letters were also sent to pharmacists, prescribing nurses (UK), wholesalers and patient advocacy groups.

6. Conclusion and grounds for the recommendation

- The Committee considered the notification of a procedure under Article 20 of Regulation EC 726/2004 triggered by the European Commission.
- The Committee reviewed all available data on the quality defect related to the formation of a flake-like precipitate of lacosamide in Vimpat syrup 15mg/ml caused by supersaturation.
- The Committee considered that the lacosamide concentration is not homogeneously distributed in the syrup due to sedimentation of the crystals of lacosamide at the bottom of the bottle and this may have an impact on the dose administered resulting in either under or overdosing with the potential consequence of Vimpat syrup 15mg/ml not being effective or increasing the risk of causing adverse events.
- The Committee also considered that there is no possible technical remediation of this defect and that the Marketing Authorisation Holder is already voluntarily recalling Vimpat syrup 15mg/ml from the market.

Therefore, in view of the available data, the Committee concluded that the benefit/risk balance of Vimpat syrup 15mg/ml is not positive under normal conditions of use.

The CHMP has therefore recommended the variation of the marketing authorisation for Vimpat to delete the syrup formulation and the amendment of the Product Information as set out in annexes I, IIIA and IIIB of the opinion.