EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for IXIARO

Review under Article 20 of **Regulation (EC) No 726/2004**

INN: Japanese encephalitis virus strain SA_{14}-14-2

Procedure number: EMEA/H/C/963/A-20/0029

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

In February 2011 the Agency was informed by the marketing authorisation holder (MAH) of an out-of-specification (OOS) result obtained during potency testing of the IXIARO batch JEV09L37 11 months after batch release (results of 1484ng and >3000ng in two consecutive assays for potency; specification is < 460ng; the assay results are expressed in reciprocal term, which means that the higher ng content the less potent the vaccine is).

According to the manufacturer, this batch had been marketed in France, Italy, Spain, UK, Canada and Australia. This particular potency test was conducted on final lot vaccine 11 months after initial release as part of an additional 'abbreviated stability testing' requested by the Canadian Competent Authority for certain IXIARO batches put on the Canadian market.

The MAH was requested to retest batch JEV09L37 11 months after batch release, and the OOS result was confirmed. All other quality assuring parameters were confirmed to be in full compliance with the approved specifications.

At the time it was not clear whether the OOS results reflected a quality defect of batch JEV09L37 only, or the loss of potency over time could be observed in other marketed batches of IXIARO.

Based on the information available at that time, it was recommended that revaccination be considered in patients who received the affected batch and envisage travelling to a country affected by Japanese encephalitis in the near future. In parallel, a recall of the affected batch was performed.

Therefore, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the CHMP to assess the impact of the OOS result observed on the safety and efficacy of IXIARO, and give its opinion on whether the marketing authorisation should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

IXIARO was first granted a marketing authorisation on 31 March 2009 and is indicated for active immunization against Japanese encephalitis (JE) in adults. It should be considered for use in individuals at risk of exposure through travel or in the course of their occupation.

JE is a mosquito-borne arboviral infection and the leading cause of viral encephalitis worldwide, with an estimate of 35000 to 50000 cases per year. It is endemic in many Asian regions such as China, Korea, Japan, South-East Asia and India. In recent years sporadic epidemics have also been noted in previously less endemic areas such as Nepal, Sri Lanka and Northern Australia.

Of the 35000 to 50000 cases of JE per year, more than 10000 are fatal, and about 15000 survivors are left with neurological and/or psychiatric sequelae requiring rehabilitation and continued care. There is currently no effective treatment for JE, so vaccination of the at-risk population is of the utmost importance.

The primary vaccination series consists of two separate doses of 0.5 ml each according to the following schedule: first dose at day 0 and second dose 28 days later.

2.1. Quality aspects

The potency assay is based on a 2nd generation potency assay, which has been implemented by further development of the original 1st generation assay. The potency specification is based on the 2nd generation potency assay and has been set at “not more than 460 ng ED50/dose”.

This particular potency test on batch JEV09L37 was conducted on this lot vaccine 11 months after initial release as part of an additional abbreviated stability testing imposed as a licensing requirement by the Canadian Competent Authority. This abbreviated stability testing was requested by the Canadian authority for those batches of IXIARO final lot vaccine, for which the potency of the final bulk vaccine is higher than 100ng. Such additional testing, at distinct time points after release, is not required for batches marketed in the EU, although selected batches continue to be tested regularly according to the real time stability program as declared in the marketing authorization dossier.

Following the detection of this out-of-specification result, a full retesting of the affected batch JEV09L37 as well as other commercially released batches of IXIARO (i.e. JEV 08L18, JEV09L38 and JEV10B46) was performed by the MAH. The re-testing included potency assay, release testing program and additional exploratory testing for detailed analysis of batch properties.

The potency failure at the 11 months time point was confirmed during the retesting exercise. IXIARO batch JEV09L37 was further confirmed to be conform in terms of the manufacture/processing tests including in-process data, test results for drug substance and drug product upon release and other stability parameters (antigen content, degree of adsorption).

A comprehensive investigation was performed on the root cause of the potency failure detected for IXIARO batch JEV09L37 after 11 months of storage. In a series of experiments the company could demonstrate that the quality of the aluminium hydroxide lot 4230 used for formulation is the most probable root cause for the potency failure seen for batch JEV09L37. The most significant effect with regard to antigen degradation was detected with the adjuvant aluminium hydroxide (AlOH) Lot 4230 (containing increased residual Cr, Fe, Ni and Cu) with the help of an ELISA test. Formulations made with AlOH Lot 4074 (which demonstrated a higher purity with regard to residual metals) generally showed a much higher ratio of specific epitope content compared to lots manufactured with AlOH Lot 4230. Of note, the affected batch of IXIARO batch JEV09L37 was manufactured using AlOH Lot 4230.

On the basis of these results, a mechanism is proposed by which the very high metal ion (and particularly Cu(II)) content of AlOH lot 4230 leads to a partial degradation of JEV antigen in the vaccine leading to a less antigenic potential, at least in the mouse model assay. The following experimental evidences have been gathered to support these conclusions:

- Metal ion content in AlOH lot 4230 has been determined and compared to other AlOH batches. Lot 4230 has a much higher metal ion concentration (in particular Cu(II) and Ni(II) ions) than other AlOH lots.
- Spiking of drug substance material with different amounts of metal ions leads to an enhanced degradation of JEV antigen. This was shown using a newly developed ELISA method in which a monoclonal antibody is employed to detect the conformational integrity of a neutralising epitope of the JEV E-protein. This ELISA method could be a very useful tool to study degradation processes in the vaccine and to detect premature loss of immunogenicity.
- Other factors can contribute to antigen degradation (such as low pH) but the AlOH quality was identified to be the key determinant.

- Differential antigen degradation was also observed when IXIARO batches, formulated with different batches of AlOH, were analyzed by ELISA method. Only those batches formulated with AlOH lot 4230 showed enhanced epitope degradation.
- Most importantly, test formulations made with the same drug substance but different AlOH batches were tested after 1 month and 20 months of storage for in vivo potency. A greatly reduced potency was detected after 20 months only for the formulation made with AlOH lot 4230. No such effect was seen with other AlOH batches, despite the inherent variability of the assay.
- Ammonia alum solution, which is one starting material for AlOH manufacturing, was identified as the source of the metal ion contamination. The ammonia alum used for manufacture of AlOH lot 4230 was very different – in metal ion content and even in its physical appearance – from other batches. Nevertheless, the AlOH lot 4230 was compliant with the current Ph. Eur. Monograph.
- AlOH lot 4230 was used in the production of final vaccine lots JEV09L37, JEV10B46 and JEV09M42. These batches of IXIARO are all beyond their period of shelf life expiry. AlOH lot 4230 was also used in the production of final vaccine lots JEV09K33 and JEV09K35, which have been used in clinical studies.

These results provide convincing evidence that the quality of the AlOH lot 4230 is the actual root cause for the JEV09L37 potency failure after the 11 months of storage, due to an accelerated degradation of the epitope of interest.

Further support for this conclusion was generated from other aspects reviewed during this procedure, in particular the critical review of the filling process which was initially assumed to be part of the potential root cause. In none of these other fields of activities any deviation or critical incident was detected that could have explained the lack of potency. Homogeneity of filling into final vaccine lot containers has been confirmed by analysis of constant AlOH and JEV antigen content throughout the entire filling process.

Conclusions on Quality

A comprehensive investigation on the root cause of the potency failure detected for IXIARO batch JEV09L37 after 11 months of storage was conducted. The analysis revealed that the root cause was an isolated event and results from elevated levels of metal ions (in particular Cu(II) and Ni(II) ions) in a particular lot of aluminium hydroxide, AlOH lot 4230. In support of the identified root cause, a mechanism has been proposed by which the very high metal ion (and particularly Cu(II)) content of aluminium hydroxide lot 4230 leads to a partial degradation of JEV antigen in the vaccine leading to a less antigenic potential, as detected in the mouse model assay. Other potential root causes initially identified, including the filling process, could be excluded based on a review of all processes and operations at the filling site.

In order to control the quality of AlOH regarding the metal ion content for future production of IXIARO, additional controls and release specifications will need to be introduced to assure the consistency and quality of ammonia alum lots for the production of future batches of IXIARO. Each lot of AlOH will have to be tested prior to ensure that only suitable lots are used for finished product production.

Until regulatory approval of the variation on specifications for metal ion content of AlOH is finalised, batch release should only be performed when potency is established to be ≤100ng, and all batches should be retested for compliance with this limit 6 months after the initial release. This measure has been voluntarily put in place by the MAH over the course of this investigation, and should continue in place until the appropriate specifications can be defined for the AlOH used as adjuvant in the production of the vaccine.

2.2. Clinical aspects

In view of the OOS result with batch JEV09L37, it was investigated whether the use of the AlOH lot 4230 had any impact on immunogenicity results obtained with IXIARO.

Post marketing data

A search of the MAH's pharmacovigilance database identified no reports of Japanese encephalitis or suspected JE in any recipient of any lot of IXIARO, including recipients of batch JEV09L37.

Three reports of seroconversion test negative/antibody test negative have been received since the marketing authorisation was first granted. These cases did not cluster in a certain period of time or with particular batches, and lot JEV09L37 was not involved in any of them.

Given the overall estimate number of vaccinees exposed to IXIARO at the time that the OOS issue was detected, the number of seroconversion reports is within expectations. In the pivotal immunogenicity trial reflected in the Summary of Product Characteristics, 3.6% of volunteers failed to seroconvert.

Clinical trials

Two batches of IXIARO formulated with the AlOH lot 4230 were used in clinical trials (JEV09K33 and JEV09K35).

Study IC51-322

This is an open-label, single arm study planned to recruit 100 children aged from 2 months to <18 years. IC51-322 is currently ongoing and is conducted in Germany, Sweden, Australia and the United States. Children received a dose on days 0 and 28, and are followed up for safety and immunogenicity on day 56 and month 7.

Thirty-four subjects in the study received two doses of JEV09K35 at time points between 9 and 18 months after formulation of the lot. A preliminary statistical analysis of the immunogenicity data available for these subjects indicates that 100% achieved the protective titer of PRNT50≥1:10. There was no apparent decline in individual titers when plotted against the data of vaccination (which reflects time elapsed since formulation of the lot). Based on the data available, it can be concluded that seroconversion rates (SCR) were comparable to those achieved in the trials in adults.

As with SCR, geometric mean titers (GMT) were also comparable to those achieved in trials in adults. Stratification of GMTs by vaccine lot and subject age did not reveal any meaningful differences.

Study IC51-323

This study is part of the paediatric investigation plan for IXIARO. It is an open label, randomized, active controlled phase III study in 1869 children aged ≥2 months to <18 years of age. Subjects are randomized to receive either IXIARO or Havrix 720. IXIARO is administered on days 0 and 28, and all children are followed up for safety. A subgroup is also followed for immunogenicity on day 56 and month 7. The database for IC51-323, which was conducted in the Phillipines, has been locked and the final analysis according to the statistical analysis plan is currently ongoing.

In this study, 463 vaccinations with JEV09K35 were given at a time point between 9 to 10.5 months after formulation. One hundred and fifteen children (13 from the immunogenicity group) received two doses of JEV09K35, 212 children (53 from the immunogenicity group) received only the first dose from

this lot, and 21 children (4 from the immunogenicity group) received only the second dose from this lot.

A preliminary statistical analysis of the immunogenicity data available indicates that 100% achieved the protective titer of PRNT50≥1:10. Based on the data available, it can be concluded that SCR were comparable to those achieved in the trials in adults.

As with SCR, GMT were also comparable to those achieved in trials in adults, regardless of whether subjects were administered 1 or 2 doses of JEV09K35. Stratification of GMTs by vaccine lot and subject age did not reveal any meaningful differences.

Study IC51-315

IC51-315 is an open label, uncontrolled phase IV study to assess the safety and immunogenicity of IXIARO in an elderly population of 200 subjects aged ≥65 years. IXIARO is administered on the standard posology (days 0 and 28), immunogenicity is followed-up on day 70 and safety is followed-up until month 7. All 200 subjects received two doses of JEV09K33, at time points between 6.5 and 16 months after formulation.

The database for the study has been locked and the final analysis according to the statistical analysis plan is currently ongoing. Based on the data available, SCR was 65% which is lower than the existing elderly datasets from previous phase III studies.

Likewise, the GMT in IC51-315 of 37 was lower compared to previous results obtained in the elderly population.

A stratification of the preliminary SCR and GMT values by age group did not reveal meaningful differences. There was no apparent decline in individual titers when plotted against the data of vaccination (which reflects time elapsed since formulation of the lot).

Conclusions on Efficacy

Information from post marketing reports and from the paediatric clinical trial is not indicative that the batches formulated using AlOH lot 4230 were impacted in terms of immunogenicity. While this information is reassuring, the statistical analysis is preliminary and the number of subjects considered is low (less than 50 individuals aged <3 up to <18 years).

Unlike the JEV09K35 lot used in the paediatric trials, which was not re-tested after release for compliance with the potency specifications, lot JEV09K33 used in study IC51-315 was shown to be within specification throughout the shelf life, although close to the upper limit of 460 ng. Clinical results obtained with this lot deviate from previous data in the elderly, although it is recognised that previous datasets involved a much lower number of patients. Low potency lots of IXIARO are probably inadequate for an elderly population, but whether or not the use of the AlOH lot 4230 in the formulation is responsible for the lower clinical performance in this population cannot be concluded. But if low potency *per se* was to be responsible for these results, then the impact on immunogenicity would be expected to be seen across age ranges and not just in a specific subset of the population.

3. Overall discussion and conclusion

Data submitted and assessed in the framework of this procedure provide convincing evidence that the quality of AlOH lot 4230 is the root cause for the potency failure of IXIARO batch JEV09L37 at 11 months of storage.

Clinical information from both the post marketing setting and clinical trials does not seem to indicate any impact of this potency failure episode on immunogenicity in humans. There is no evidence of breakthrough infections or lack of seroconversion being higher than would be expected in the general population. On the basis of the currently available information, a recommendation for revaccination does not appear necessary.

No IXIARO batches formulated using the affected AlOH lot and within expiry date are currently on the market. Therefore no additional batch recall is needed.

While this potency failure is considered to be an isolated event, to ensure that IXIARO continues to provide adequate protection against the Japanese encephalitis virus it is necessary that studies are conducted to establish an adequate set of specifications for the metal ion content of AlOH used in the manufacture of IXIARO, and that a variation application be submitted to introduce the new specifications in the marketing authorisation dossier. Until the approval of this variation application, potency should be demonstrated to be ≤100ng at batch release, and all batches should be retested for compliance with this limit 6 months after the initial release.

Notwithstanding the fact that the benefit-risk balance of IXIARO is considered to be positive subject to the conditions described above, the CHMP recommends that the MAH puts in place a recall study to investigate immunogenicity in patients exposed to at least one dose of the IXIARO batch JEV09L37. The study should be completed by end of 2012 and interim reports should be provided to the CHMP at monthly intervals.

4. Conclusion and grounds for the recommendation

Having considered the overall submitted data provided by the MAHs in writing:

- The Committee reviewed the data available in relation to the out of specification result for potency identified with batch JEV09L37.
- The Committee considered that the root cause of the occurrence has been identified to be the unusually high metal ion content of a specific batch of the adjuvant AlOH, and that measures can be put in place to prevent similar occurrences in the future.
- The Committee took note of the fact that no batches formulated with the above mentioned batch of the adjuvant are currently on the market.
- Based on currently available post marketing and clinical trial data, the Committee is of the opinion that patients who received the affected batch were not clinically impacted by the out of specification result.

The Committee, as a consequence, concluded that the benefit/risk balance of IXIARO is positive, provided that adequate specifications are defined for the metal ion content of the adjuvant AlOH, and that until such specifications are established, potency testing is conducted at batch release and repeated after 6 months.

The scientific conclusions and the grounds for the amendment of Annex II are set out in Annex IV of the opinion.