CNMV
Directorate General of Markets
c/ Edison núm. 4
28006 Madrid

Madrid, November 10, 2020

In accordance with article 226 of the recast Spanish Securities Market Act (*Ley del Mercado de Valores*), is hereby reported the following

INSIDE INFORMATION

Last Friday, November 6, 2020 at 7:06 pm, Pharma Mar, S.A. (the "Company") received a request from the Directorate General of Markets of the National Securities Market Commission (CNMV), a copy of which is attached (only available in Spanish), by virtue of which the Company is required to provide a written response, before the opening of the market on November 10, in addition to the communication of Privileged Information dated October 16, 2020 (registration number 496), on the results of the APLICOV-PC clinical trial with Aplidin® (plitidepsin) for the treatment of adult patients with COVID-19, who require hospitalization.

Previously, and by means of a reply written by the Company on October 30, to a first requirement of the CNMV on October 23, about the results of the aforementioned clinical trial, the Company has already given a detailed and timely answer to the twelve questions required by the CNMV, of an eminently medical-scientific nature, more typical of the Spanish Agency for Medicines and Healthcare Products (AEMPS), which as a public body, has among its competencies, the power to "*authorize, modify, suspend or revoke clinical trials of medicines for human and veterinary use and of healthcare products*" (article 7.6 of the Royal Decree 1275/2011, of 16 September, by which the state Agency "Agencia Española de Medicamentos y Productos Sanitarios" is created and its Statute is approved), as well as to carry out the inspection and control of medicines. The questions asked by the CNMV in the aforementioned requirement were the following:

1. Indicate the number of patients who have participated in the aforementioned clinical trial.

2. Indicate the age distribution of these patients and data on their initial prognosis, including a description of the risk factors present at the beginning of the study.

3. Specify if any of the patients decided to abandon the study, showed side effects or died during the trial.

4. Specify whether any of the patients required ICU admission or mechanical ventilation.

5. State whether the statement in the press release that the expansion of the patient cohort has been requested in order to "allow access to treatment for those patients who need it" is the purpose of the requested expansion or if, on the contrary, it is justified by the need to increase the number of patients in order to correctly select the therapeutic dose given the small size of the initial sample.

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6. State whether the statement contained in the press release regarding the "remarkable parallelism between the decrease of viral load, clinical improvement and pneumonia resolution (sic)" is somehow indicative of the efficacy of the treatment in the absence of a controlled design or whether it can be a parallelism to be expected even in the natural evolution of a COVID-19 type disease.

7. Indicate if the patients received additional concomitant medication during the study and if, in that case, its impact on the evolution of the patients can be estimated.

8. Indicate if the rates offered for hospital discharge within 8 and 15 days mean a difference with respect to the average rates of discharge within those periods for patients with COVID-19 with similar characteristics to those who participated in the trial in the hospitals taking part in the study.

9. Indicate if the extension granted by the Spanish Agency of Medicine regarding the extension of the patient cohort suggests or implies any type of support or validation of the treatment's efficacy.

10. Regarding the affirmation that the activity of the drug "...has already been seen in in vitro and in vivo studies in different laboratories of international prestige," indicate which public and contrastable sources on the activity of the in vivo drug can be consulted by the public and if they have been the object of publication in scientific journals.

11. Indicate if you have already submitted for publication in scientific journals and/or congresses the complete and detailed results of the study and, in that case, to which journals or congresses and on which dates they have been submitted.

12. Indicate if, on the date of your reply, you have requested or initiated conversations with any regulatory agency for an eventual phase III study and, in that case, name of the agency and date of the request.

In this response to the request, information and data of a sensitive and strictly confidential nature were provided which, if published at this time, could seriously damage the business interests of Pharma Mar with regard to its competitors, as well as seriously compromising their dissemination through journals and/or scientific conferences which require that they have not been previously published.

Without prejudice to the above, the Company, in response to the requirement of the CNMV last Friday, November 6, proceeds to answer all the questions raised in the same, following the same order provided in the requirement:

1. Whether the clinical trial had a randomized control arm that allows to conclude that the clinical and viral load improvement, as well as the hospital discharge rates, are attributable to Aplidin.

APLICOV-PC clinical trial, for the treatment of adult patients with COVID-19, who require hospital admission, is a phase I/II trial whose primary objective was to characterize the safety profile of plitidepsin (Aplidin®) at three different doses, 1.5mg, 2mg and 2.5mg, during three consecutive days. As it is well known, this type of Phase I/II trials with a primary safety profile objective do not have a control arm since it does not require comparison with other treatments. Therefore, this clinical trial did

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not have a control arm. On the other hand, the trial also had a secondary objective of plitidepsin activity against COVID-19. Therefore, although this trial did not have a control arm, the observation of acute drops of viral load, which is indicative of the "volume" of the disease, we consider it a pharmacological effect on viral replication. Moreover, this dynamics is observed accompanied by clinical improvement, impact on inflammatory markers (C-reactive protein) and radiological improvement, which are indicators of efficacy as well as the only antiviral product approved for the treatment of COVID-19, Gilead remdesivir, mentioned below in response to question number 2.

On the other hand, it should be pointed out, as expressly established by the AEMPS in the official document entitled "*How are medicines and products regulated in Spain*" published on its web page, that the trials of medicines for human use *in phase II are exploratory of efficacy*. In line with this, for more than twenty years the Company has been reporting the results of phase I/II of its oncological products, highlighting activity where it existed (overall survival, response rate, time to progression, progression-free disease, etc.). It should also be noted that even phase II studies without randomized trials can be used to approve a drug for its efficacy, proof of which is that on June 16, 2020, the FDA approved Pharma Mar's compound lurbinectedin under an accelerated procedure for the second line treatment of small cell lung cancer based on a phase II without a control arm.

Therefore, the Company, as informed in the insider's communication to the CNMV and in the press release attached to it, dated October 16, 2020, *"will start conversations with the regulatory agencies to define the next phase III study for the registration of plitidepsin in patients with COVID-19 who require hospitalization"*. The realization of a phase III requires a very high level of investment by the Company, so we would not start a phase III if there were no evidence of safety and efficacy, and the belief that it can be better than the control arm in a clinically meaningful way.

2. In the absence of a control arm, based on what they consider that the test performed has confirmed the activity of Aplidin in relation to COVID-19.

Viral load data alone are not considered indicative of efficacy, however, in the COVID-19 drug development program, as suggested in the application guidelines (COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration, May 2020) the effect on clinically significant aspects of the disease should be evaluated, such as, among others, the modulation of inflammation and the clinical evolution of patients observed favorably in this study with the use of plitidepsin.

In the APLICOV-PC study, the determination of viral load updated to date, taking into account the extension of the trial, has been carried out in a centralized way in samples of 37 out of 45 patients. As we have indicated in the answer to the previous question, as it is a phase I/II, there is not a control arm in the trial; however, the observation of acute drops of viral load, which is indicative of the "volume" of the disease, we consider it a pharmacological effect on viral replication. This dynamic is observed accompanied by clinical improvement, impact on inflammatory markers (C-reactive protein), radiological improvement and hospital discharge.

It is important to highlight that there are data already reported in the study ACTT-1 code NCT 04280705, *Remdesivir for the Treatment of Covid-19 - Final Report (J.H. Beigel et al, October 9, 2020*) for a population equivalent to that included in the APLICOV-PC study when we classified the 27 initial patients according to the ordinal scale used in that study and which has been referenced in the approval in the United States of remdesivir (*Reference ID: 4689430 NDA 214787: Cross Discipline Team Leader, Division Director and ODE Director Summary Review*).

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From the above-mentioned ACTT-1 study patient population that received a score of 4 (hospitalized patients not requiring oxygen but requiring medical treatment for COVID-19 - concomitant pathologies) or 5 (hospitalized patients requiring supplemental oxygen) at the time of study inclusion At the end of the study, 37.45% of those who received a placebo, and 44.75% of those who took remdesivir, were reclassified receiving a score of 1 on the ordinal scale mentioned, or in other words, they were discharged without functional limitations on the 15th day (+/- 2 days). In the APLICOV-PC study (APLD-D-002-20), 80.76% (21 patients out of a total of 26 evaluable) of the population equivalent to the one described above, that is, patients who received a score of 4 or 5 upon inclusion and who were given plitidepsin, were discharged from the hospital on a day equal to or less than 15. With regard to the score scale 1, the following table is attached:

% discharge without functional limitations to Day 15 (score 1 on the ordinal scale)		
Study NCT 04280705 Placebo	Study NCT 04280705 Remdesevir	Study APLD-D-002-20 Plitidepsina
37,4%	44,75%	80,76%

3. If the above mentioned trial allows to conclude that Aplidin is an effective medicine against COVID-19.

As we have indicated in the answers to the previous questions, the APLICOV-PC clinical trial has been a phase I/II trial, its primary objective being to measure the safety profile of plitidepsin (Aplidin®) at three different doses, without the use of a control arm, as it is not required to be compared with other treatments. Nevertheless, our clinical trial model, through the proposed doses, has allowed to evidence the antiviral activity of plitidepsin in the context of COVID-19 disease, by acting on viral multiplication. This was already stated by Dr. José Jimeno, head of Virology at Pharma Mar, in the presentation of the preliminary results of the clinical trial that took place on October 19, 2020, at the Hospital Universitario de La Princesa in Madrid, when he indicated "*I am only going to comment that the primary objective has been fulfilled which was to demonstrate that the proposed doses of aplidin in this clinical condition are safe, That is clearly demonstrated, our model anticipated that those doses should reach therapeutic concentrations in tissues relevant to the context of the disease, our model of therapeutic intervention is based on the antiviral activity of plitidepsin, that is, act on viral multiplication, and that evidence has been generated.*"

The referred presentation of preliminary results of the clinical trial in the University Hospital of La Princesa of Madrid, was carried out through a press conference, in which together with the Minister of Health of the Community of Madrid, Mr. Enrique Ruiz Escudero, some of the researchers participating in the study appeared: Dr. Pedro Landete, pneumologist of the Hospital Universitario de La Princesa; Dr. Vicente Estrada, internist of the Hospital Universitario Clínico San Carlos; Dr. José Barberán, specialist in Infectious Diseases of HM Hospital Montepríncipe and Dr. José Jimeno, head of Virology of Pharma Mar.

In the same line as previously stated by Dr. Jimeno, Dr. Vicente Estrada stated: "*The truth is that it is a drug that is well-tolerated, there are no relevant adverse effects that have forced the suspension of the medication and the data on the viral loads of the COVID are quite favorable, that is, the viral load is reduced, so it is a drug that has an enormously promising aspect. Obviously until we compare*

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ourselves to the standard we will not be able to say anything for sure, but of course the preliminary data are very encouraging and that is what I simply want to say, the truth". "(...) if it is possible to control the disease by inhibiting viral replication with this drug, it is clear that the disease is not going to progress (...)"

Furthermore, in the aforementioned presentation it was clearly stated by several of the participants that in this phase II the primary objective of the drug was to evaluate its safety, and as a secondary objective its efficacy, so that later in a phase III we can compare it with other treatments, and thus better evaluate the efficacy of the drug.

Likewise, Dr. Jose Barberán stated the following: "*I believe we are looking at a very promising drug, I believe it is a drug that could be the first to have antiviral activity, it is a drug that could be initiated in the early phase and could prevent many side effects, that inflammatory phase that we have and that unfortunately takes many patients because of this inflammatory effect, and nothing else.*"

The Company wants to state that its partner Boryung Pharmaceutical will start soon clinical trials with plitidepsin in COVID-19 in South Korea, convinced of its activity tested by the Pasteur Institute, verified by Mount Sinai Hospital in New York and confirmed by APLICOV-PC clinical trial. Also, the Company at the request of its partners has sent all the information to Megapharm, Specialised Therapeutics Asia (STA), TTY Biopharm, and of course to the AEMPS.

The Company is all that it can say so far about the efficacy of plitidepsin (Aplidin®), and cannot conclude any further until it obtains phase III results.

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Madrid, 6 de noviembre de 2020

Estimados Sres.:

Nos referimos a su respuesta de fecha 29/10 al requerimiento del día 23/10 sobre la publicación como información privilegiada el 16/10 de una descripción de los resultados de un ensayo con el compuesto denominado Aplidin en pacientes de COVID-19 en algunos hospitales españoles, en la que incluyeron una nota de prensa.

Dicho anuncio, titulado "La sociedad anuncia resultados positivos de su ensayo APLICOV contra la COVID-19" indica que el ensayo "ha alcanzado los objetivos primario de seguridad y secundario de eficacia". Los párrafos siguientes de la comunicación tratan principalmente sobre el objetivo, que se califica como secundario, de eficacia. En ellos se describe en detalle cómo se redujo la carga viral de los pacientes que, en su gran mayoría, fueron dados de alta. Asimismo, se destaca el paralelismo notable entre dicha reducción de la carga viral y la mejoría clínica, la resolución de la neumonía y la caída de parámetros de inflamación. El mensaje de reducción de la carga viral se reitera en la nota de prensa.

Analizada dicha respuesta, se considera que la información publicada en el 16/10, no contenía el detalle necesario para considerar la información completa.

En atención a ello, en virtud de lo establecido en el artículo 23.2 letra m) del Reglamento UE 596/2014 de Abuso de Mercado y en el artículo 237 del Texto Refundido de la Ley del Mercado de Valores (aprobado por Real Decreto Legislativo 4/2015, de 23 de octubre), se les requiere para que publiquen antes de la apertura del mercado del próximo día 10 de noviembre una comunicación de información privilegiada, complementaria de la publicada el día 16/10, que indique de modo conciso y expreso:

1. Si el ensayo clínico contó con un brazo de control randomizado que permita concluir que la mejora clínica y de la carga viral, así como las tasas de alta hospitalaria, son atribuibles al Aplidin.

2. En ausencia de brazo de control, con base en qué consideran que el ensayo realizado ha confirmado la actividad del Aplidin en relación con la COVID-19.

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3. Si el mencionado ensayo permite concluir que Aplidin sea un medicamento eficaz contra la COVID-19.

La comunicación complementaria que publiquen deberá adjuntar copia de este requerimiento.

Les recordamos que la normativa citada habilita a la CNMV a publicar esas informaciones si el emisor no lo hiciese.

Para cualquier duda con relación a este requerimiento también pueden ponerse en contacto con el Subdirector de Renta Variable del Departamento de Mercados Secundarios.

Atentamente,

Javier Ruiz del Pozo
Director de Mercados Secundarios
P.D. del Director General de Mercados (Resolución 01/07/2020)

Firmado electrónicamente
Datos de la firma en el documento electrónico