Esmya: new measures to minimise risk of rare but serious liver injury

08/08/2018

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EMA concludes review of medicine for uterine fibroids

On 31 May 2018, the European Medicines Agency (EMA) recommended that several measures be put in place to minimise the risk of rare but serious liver injury with Esmya (ulipristal acetate). Certain women may start treatment with Esmya once the new measures are implemented.

The measures include: contraindication in women with known liver problems; liver tests before, during and after stopping treatment; a card for patients to inform them about the need for liver monitoring and to contact their doctor should they develop symptoms of liver injury. In addition, use of the medicine for more than one treatment course has been restricted to women who are not eligible for surgery.

Esmya is used to treat moderate to severe symptoms of uterine fibroids (benign tumours of the womb). The medicine has been shown to be effective at reducing bleeding and anaemia associated with the condition, as well as the size of the fibroids.
The review of Esmya was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) following reports of serious liver injury, including liver failure leading to transplantation. The PRAC concluded that Esmya may have contributed to the development of some cases of serious liver injury.[1]

The PRAC therefore recommended that use of the medicine should be restricted. It also recommended that studies should be performed to determine the effects of Esmya on the liver and whether the new measures are effective in minimising the risks.

The PRAC's recommendations were endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP) and sent to the European Commission for a final legal decision. A letter was sent to doctors to inform them of the new conditions of use.

Information for patients

- The medicine Esmya, used to treat uterine fibroids, has been reviewed because cases of serious liver problems have occurred in women taking the medicine, including four cases that resulted in liver transplantation.

- Esmya will not be prescribed to you if you have liver problems.
- A liver test will be performed before you start treatment and if the test is abnormal, treatment with Esmya will not be started.
- You will also have liver tests during treatment and after treatment has stopped.
- If no liver problems are detected, a single course of Esmya can be used in women who are about to have surgery for their fibroids; Esmya can be used for more than one course only in women who cannot have surgery.
- A card will be included in the package of the medicine with information on the risk of liver injury and the need for liver monitoring.
  • You should stop treatment and contact your doctor immediately if you develop symptoms of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting).
- If you have any questions or concern about your treatment, speak to your doctor or pharmacist.

Information for healthcare professionals

- Four cases of serious liver injury leading to hepatic transplantation and additional cases of hepatic injury have been reported in patients treated with Esmya (ulipristal acetate). Although uncertainties around causality remain, the following measures to minimise a possible risk for liver injury have been introduced:
  - Contraindication in patients with underlying liver disorders.
  - Restricted indication in the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age: Esmya should only be used in women who are not eligible for surgical treatment. (Esmya continues to be indicated for one course (lasting up to 3 months) of pre-operative treatment for moderate to severe symptoms of uterine fibroids in adult women of reproductive age.)
  - Liver function tests to be performed before starting each treatment course, monthly during the first 2 treatment courses, and thereafter as clinically indicated. Liver testing also to be performed again 2-4 weeks after stopping treatment.
  - Esmya should not be started if levels of alanine transaminase (ALT) or aspartate aminotransferase (AST) are more than 2 times the upper limit of normal (ULN).
  - Treatment should be stopped in patients with ALT or AST levels more than 3 times ULN.
- Healthcare professionals should advise their patients about the signs and symptoms of liver injury and the action to take should they occur. In case of signs or symptoms suggestive of such injury, treatment should be stopped. Patients should be investigated immediately including liver function testing.
- Healthcare professionals prescribing Esmya in the EU have been sent a letter with further details.

More about the medicine

Esmya was authorised in the EU in 2012 for the treatment of moderate to severe symptoms of uterine fibroids, which are benign (non-cancerous) tumours

of the womb, in women who have not reached the menopause.
The active substance in Esmya, ulipristal acetate, works by attaching to the targets on cells (receptors) that the hormone progesterone normally attaches to, preventing progesterone from having its effect. Since progesterone may promote the growth of fibroids, by preventing the effects of progesterone ulipristal acetate reduces the size of the fibroids.

Ulipristal acetate is also the active substance of a single-dose medicine authorised for emergency contraception, ellaOne. No cases of serious liver injury have been reported with ellaOne and there are no concerns with this medicine at this time.

More about the procedure

The review of Esmya was initiated at the request of European Commission on 30 November 2017, under Article 20 of Regulation (EC) No 726/2004.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines.

While the review was ongoing, the PRAC had issued temporary recommendations that no new patients should start treatment.

The PRAC issued its final recommendations on 17 May 2018, replacing the temporary measures. The PRAC's final recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted an opinion.

The CHMP opinion was forwarded to the European Commission, which issued a final legally binding decision applicable in all EU Member States on 26/07/2018.

123/2018 : 7 August 2018 – Judgment of the Court of Justice in Case C-161/17

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Updated Blocking Statute in support of Iran nuclear deal entered into force

As the first batch of re-imposed US sanctions on Iran took effect, the EU's

updated Blocking Statute entered into force early today to mitigate their impact on the interests of EU companies doing legitimate business in Iran. The updated Blocking Statute is part of the European Union's support for the continued full and effective implementation of the Joint Comprehensive Plan of Action (JCPOA) – the Iran nuclear deal, including by sustaining trade and economic relations between the EU and Iran, which were normalised when nuclear-related sanctions were lifted as a result of the JCPOA. A press release and a MEMO Q&A are available online, as well as the joint statement by High Representative/Vice-President Federica **Mogherini** and the Foreign Ministers of the E3 (Jean-Yves Le Drian of France, Heiko Maas of Germany, Jeremy Hunt of the United Kingdom) on the re-imposition of US sanctions due to its withdrawal from the JCPOA. You can find all relevant information on the updated Blocking Statute on a dedicated website here, and the Updated annex of the Blocking Statute, the Guidance note and the Implementing Regulation on the criteria are available online. *(For more information: Mina Alexandrova Andreeva – Tel.: +32 229 91382; Maja Kocijancic – Tel.: +32 229 86570; Lauranne Devillé – Tel.: +32 229 80833)*

Roumanie: l'UE investit dans le transport fluvial de la Mer Noire au Danube

59 millions d'euros du Fonds de Cohésion sont investis dans la modernisation des écluses sur les canaux "Danube – Mer Noire" et "Midia Navodari – Porte Blanche" qui relient le port de Constanța, au bord de la Mer Noire, au fleuve Danube dans le Sud-Est du pays. Les travaux permettront d'augmenter le trafic de bateaux de près de la moitié de ce qu'il est actuellement, tout en améliorant la sécurité de la navigation et en protégeant les alentours des inondations. La Commissaire à la politique régionale Corina Creţu a commenté: *"Ce projet permettra d'exploiter davantage l'énorme potentiel du transport fluvial en termes d'échanges commerciaux. C'est toute l'économie du Sud-Est de la Roumanie qui en bénéficiera mais aussi, plus largement, l'économie de la macro-région du Danube, qui lie neuf Etats membres de l'UE et cinq pays voisins."* Les canaux font en effet partie du Réseau Transeuropéen de Transport, sur la section qui relie le Rhin au Danube. Les travaux devraient être achevés en 2021. *(Pour plus d'informations: Johannes Bahrke – Tel.: +32 229 58615, Sophie Dupin de Saint-Cyr – Tel.: +32 229 56169)*

Juncker Plan guarantees largest ever EIB support for agri-business in Ireland

The European Investment Bank (EIB) has signed a €40 million financing agreement with agri-technology company Devenish Nutrition which is guaranteed under the Juncker Plan's European Fund for Strategic Investments (EFSI). The company, which is based in Belfast and has manufacturing sites across Ireland and other countries, will use the long-term financing for its research, development and growth plans. Thanks to the EIB's investment, Devenish also secured two new commercial finance partners, Ulster Bank and Danske Bank, bringing their total financing injection to €118 million. Devenish aims to add over 100 new jobs to its current 450-strong international employee base by 2021. Commissioner Phil **Hogan**, responsible for Agriculture, said: "*The*

Irish agri-business sector contributes enormously to the Irish economy and particularly to the rural economy. There are huge opportunities for companies like Devenish who have a vision for the future, but they are operating in a highly competitive environment, where investment, particularly in research and innovation is essential to maintain a competitive edge. Today's announcement by the EIB under the Investment Plan for Europe is very welcome, coming at a time of some uncertainty for the Irish agri-business sector. It is a strong statement of confidence in the resilience of the sector and its capacity to grow and reach its full potential. The EIB's investment is an obvious statement of confidence in Devenish's ambition, but it is also a very tangible vote of confidence in Irish agri-business and its potential to benefit from new and emerging global opportunities, particularly given the important emphasis that Devenish places on sustainability." (Full press release can be found here. For more information: Christian Spahr – Tel.: +32 229 50055; Siobhán Millbright – Tel.: +32 229 57361)

European Public Prosecutor's Office: Malta becomes 22nd country to join common efforts to protect EU budget against fraud

Only a week after the Netherlands joined the European Public Prosecutor's Office (EPPO), the European Commission can confirm today Malta as its 22nd member. EU Commissioner for Justice, Gender Equality and Consumers, Vera **Jourová**, said: *"I am very pleased to receive Malta as a member of the EPPO. A month ago, I met with the Maltese authorities. They reaffirmed their will to fight crimes against the EU budget. We can do this together through the EPPO. This is why I urge all remaining Member States to join in. The more Member States participate in the EPPO, the stronger the Office will be."* The EPPO will play a key role in fighting crimes against the EU budget such as fraud, corruption, money laundering or serious cross-border VAT fraud above €10 million. It will be operational by the end of 2020 in all participating EU Member States. Member States that have not yet chosen to participate in the European Public Prosecutor's Office can join at any time after the adoption of the Regulation, if they wish to do so. The following EU countries are already participating to the EPPO: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Greece, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Romania, Slovakia, Spain and Slovenia. The decision is published here and will be published in the Official Journal tomorrow. More information on EPPO is available in this memo, and more information on enhanced cooperation is available in this factsheet. (*For more information: Nathalie Vandystadt – Tel.: +32 229 67083; Sara Soumillion – Tel.: + 32 229 67094*)

€15 million of EU financing for micro-entrepreneurs in Latvia under the Juncker Plan

The European Investment Fund (EIF) and ALTUM, a state-owned development institution of Latvia, have signed a microfinance guarantee agreement under the EU Programme for Employment and Social Innovation (EaSI). Thanks to this agreement, micro-entrepreneurs will be able to benefit from loans at a reduced interest rate with lower collateral requirements under the EU supported programme. More specifically, this new EaSI guarantee agreement allows ALTUM to provide such loans to 600 micro-entrepreneurs over the next 3

years in all regions of Latvia. ALTUM will primarily target start-ups and businesses with small turnover. This new financing agreement was made possible by the European Fund for Strategic Investments (EFSI), the core of the Investment Plan for Europe. Commissioner for Employment, Social Affairs, Skills and Labour Mobility, Marianne **Thyssen**, said: "*With the help of EU funding, ALTUM will improve access to finance for about 600 micro-enterprises in Latvia, many of whom face difficulties in accessing credit from traditional banking sources. This new EaSI guarantee agreement will allow micro-entrepreneurs to benefit from loans with favourable conditions. This shows again that the European Commission, through the EaSI programme, is fully committed to boosting employment in Europe and getting more people into jobs*." The full press release can be found here. *(For more information: Nathalie Vandystadt – Tel.: +32 229 67083; Sara Soumillion – Tel.: + 32 229 67094)*

Mergers: Commission clears acquisition of Gorenje by Hisense

The European Commission has approved, under the EU Merger Regulation, the acquisition of sole control over Gorenje gospodinjski aparati of Slovenia by Hisense Group of China. Both companies produce and supply large domestic appliances, such as refrigerators or ovens. The Commission concluded that the proposed transaction would raise no competition concerns given the companies' limited combined market positions and the fact that a number of competitors would remain in the market post-transaction. The transaction was examined under the simplified merger review procedure. More information is available on Commission's competition website, in the public case register under the case number M.8976. *(For more information: Ricardo Cardoso – Tel.: +32 229 80100; Giulia Astuti – Tel: +32 229 55344).*

Mergers: Commission clears acquisition of Federal-Mogul by Tenneco

The European Commission has approved under the EU Merger Regulation the acquisition of Federal-Mogul LLC by Tenneco Inc., both of the US. Federal-Mogul is active worldwide in the manufacturing and distribution of components for motor vehicles, rail and other applications, in particular concerning powertrain and motor parts products. Tenneco manufactures and distributes components for motor vehicles worldwide, in particular clean air and ride performance products, such as exhaust systems and suspension technologies. Both companies are active in the production and distribution of various automotive components. However, their product portfolios in the European Economic Area are, to a large extent, complementary. In this respect, there are no significant horizontal overlaps between their activities with regard to individual components. Therefore, the Commission concluded that the proposed acquisition would not raise competition concerns. The transaction was examined under the normal merger review procedure. More information is available on the Commission's competition website, in the public case register under the case number M.8949. *(For more information: Ricardo Cardoso – Tel.: +32 229 80100; Giulia Astuti – Tel: +32 229 55344).*

Upcoming events of the European Commission (ex-Top News)

ESMA RESPONDS TO EIOPA QUESTIONS ON AIFMD

ESMA responds to the questions raised by EIOPA under section 11.5.2. of its second set of advice to the European Commission on specific items in the Solvency II Delegated Regulation (EIOPA-BoS-18/075). In this context, EIOPA addressed several questions to ESMA with respect to the AIF definition and leverage calculation pursuant to the Alternative Investment Fund Managers Directive (AIFMD) and its implementing measures.

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