European Medicines Agency

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This product was later resubmitted to the EMEA.
See here for information on the outcome of the resubmission.

QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF THE MARKETING APPLICATION for DUOPLAVIN

International non-proprietary name (INN): ***clopidogrel/acetylsalicylic acid***

On 23 May 2008, Sanofi Pharma Bristol-Myers Squibb officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for DuoPlavin for the prevention of atherothrombotic events.

What is DuoPlavin?
DuoPlavin is a medicine containing the active substances clopidogrel and acetylsalicylic acid in one tablet. It was to be available as tablets containing 75 mg clopidogrel plus 75 mg acetylsalicylic acid, and as tablets containing 75 mg clopidogrel plus 100 mg acetylsalicylic acid.

What was DuoPlavin expected to be used for?
DuoPlavin was expected to be used in adult patients already taking clopidogrel and acetylsalicylic acid as separate tablets. It was expected to be used to prevent atherothrombotic events (problems caused by blood clots and hardening of the arteries) in patients who have a condition known as 'acute coronary syndrome'. This included patients who were having an acute myocardial infarction (heart attack) with an 'ST segment elevation' (an abnormal reading on the electrocardiogram or ECG) when the doctor thought that they would have benefited from the treatment. It was also expected to be used in patients who did not have this abnormal reading on the ECG, if they had unstable angina (a severe type of chest pain) or a 'non-Q-wave' myocardial infarction and who had a stent inserted (a short tube placed in an artery to prevent it closing up).

How is DuoPlavin expected to work?
The active substances in DuoPlavin, clopidogrel and acetylsalicylic acid, are combined into one tablet in DuoPlavin to reduce the number of tablets the patients need to take every day. It was hoped that this would make it easier for patients to stick to their treatment.
Acetylsalicylic acid is a well-known medicine, commonly known as aspirin, that has been used for a long time as a blood-thinning agent.
Clopidogrel is an inhibitor of platelet aggregation. This means that it helps to prevent blood clots from forming. When the blood clots, this is due to special cells in the blood, the platelets, sticking together (aggregating). Clopidogrel stops the platelets aggregating by blocking a substance called ADP from binding to a special receptor on their surface. This stops the platelets becoming 'sticky', reducing the risk of a blood clot forming and helping to prevent another heart attack or stroke.

What documentation did the company present to support its application to the CHMP?
Clopidogrel on its own has been approved by the EU under the names Iscover and Plavix, for prevention of atherothrombotic events, in combination with acetylsalicylic acid, in patients with acute coronary syndrome. To support the application for DuoPlavin the company carried out

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‘bioequivalence’ studies to establish whether the combined tablet was absorbed in the body in the same way as the two medicines given separately. Furthermore, the studies of Iscover and Plavix used with acetylsalicylic acid as separate tablets were used to support the use of DuoPlavin in the same indication.

How far into the evaluation was the application when it was withdrawn?
The application was at day 206 when the company withdrew.
After the CHMP had assessed the responses from the company to a list of questions, there were still some unresolved issues outstanding.
The CHMP normally takes up to 210 days to evaluate a new application. Based on the review of the initial documentation, the CHMP prepares a list of questions at day 120, which is sent to the company. Once the company has supplied responses to the questions, the CHMP reviews them and may, before giving an opinion, ask any remaining questions at day 180. Following the CHMP’s opinion, it usually takes around two months for the European Commission to grant a licence.

What was the recommendation of the CHMP at that time?
Based on the review of the data and the company’s responses to the CHMP list of questions at the time of the withdrawal, the CHMP had some concerns. However the CHMP thought that the company could have addressed these concerns and was of the provisional opinion that DuoPlavin could have been approved for the prevention of atherothrombotic events.

What were the main concerns of the CHMP?
The CHMP was concerned that the bioequivalence studies that were carried out did not use the recommended methods and did not provide sufficient evidence that the combined tablet was absorbed in the body in the same way as the two medicines given separately. Therefore, at the time of the withdrawal, the CHMP’s view was that the company had not fully addressed their concerns and the benefit of DuoPlavin combined tablet compared with the separate medicines had not been sufficiently demonstrated.

What were the reasons given by the company to withdraw the application?
The letter from the company notifying the EMEA of the withdrawal of the application is available here.

What are the consequences of the withdrawal for patients undergoing clinical trials / compassionate use programmes with DuoPlavin?
The company informed the CHMP that there are no consequences for patients who are planned to be included in clinical trials with DuoPlavin or patients currently included in clinical trials with clopidogrel and acetylsalicylic acid as separate medicines.
If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.

What is happening for Iscover/Plavix with acetylsalicylic acid for treatment of atherothrombotic events?
There are no consequences on the use of Iscover/Plavix with acetylsalicylic acid in the authorised indications, for which the balance of benefits and risks remains unchanged.