The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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EMEA PUBLIC STATEMENT ON VIRAMUNE (nevirapine)
– SEVERE AND LIFE-THREATENING CUTANEOUS AND HEPATIC REACTIONS -

The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP), has recently been made aware of additional reports of serious cutaneous and hepatic reactions, sometimes fatal, associated with Viramune[1] (nevirapine). This has led to a re-assessment the benefit risk profile of nevirapine.

This assessment confirmed that severe and life-threatening cutaneous (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) and hepatic reactions are the major clinical toxicity of nevirapine. The **first 8 weeks** of therapy with nevirapine therapy are a critical period which therefore require a close monitoring of the patients to disclose the potential appearance of severe and life-threatening skin reactions or serious hepatitis/hepatic failure. Some of the severe cutaneous reactions were associated with risk factors such as not following the dose escalation regimen or delaying seeking medical attention when the symptoms appeared. Furthermore, most of the cases of hepatitis were reported to be **within the first 8 weeks** of treatment, some of them were associated with hypersensitivity reactions (such as fever, rash, arthralgia, myalgia, hypereosinophilia or acute renal failure).

Following a review of the above information, the EMEA wishes to draw attention to the following:

- **Concerning cutaneous reactions, the initial dosing of nevirapine of 200 mg daily and for patients 2 months up to 8 years 4 mg/kg once daily during the 14-days lead-in period must be STRICTLY adhered to.**
- **Patients should be intensively monitored during the first 8 weeks of treatment. Nevirapine must be permanently discontinued in patients developing a serious cutaneous reaction i.e. Stevens-Johnson syndrome, a toxic epidermal necrolysis or a severe rash accompanied by hypersensitivity reactions (characterised by rash, constitutional symptoms such fever, arthralgia, myalgia and lymphadenopathy, and visceral involvement such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction).**
- **Concerning hepatic reactions, a close liver monitoring of patients must be performed especially during the first 8 weeks of therapy (see below). Nevirapine should be stopped and never readministered in patients with ASAT or ALAT greater than 2ULN associated with hypersensitivity reactions (characterised by rash, constitutional symptoms such fever, arthralgia, myalgia and lymphadenopathy, and visceral involvement such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction) or hepatitis.**

As an urgent measure, the prescribing and patient information has been modified through a rapid procedure at the request of the marketing authorisation holder. The EMEA thought it necessary to provide this new information to the public. The complete revised product information is available in the European Public Assessment Report of Viramune published on the EMEA Website.

[1] Viramune is a non-nucleoside inhibitor of the reverse trancriptase of the HIV virus and indicated for antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) infected patients with advanced or progressive immunodeficiency. The European Commission granted marketing authorisation for the European Union to Boehringer Ingelheim International GmbH on 5 February 1998 for the medicinal product Viramune 200 mg tablets and on 18 June 1999 Viramune 50 mg/ 5 ml oral suspension, which contains the active substance nevirapine. Viramune 200 mg tablets is marketed in all EU Member States and Viramune 50 mg/5 ml oral suspension is marketed is Austria, France, Germany, The Netherlands and United Kingdom.

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RECOMMENDATIONS FOR LIVER MONITORING

Monitoring of hepatic function must be performed every two weeks during the first 2 months of treatment, at the 3rd month and then on a 3-6 monthly basis. It is also recommended that monitoring of the liver function should also be performed if the patient experiences signs or symptoms suggestive of a hepatitis and/or hypersensitivity reactions.

Activity of aminotransferases	**Clinical symptoms of hypersensitivity** **(Such as fever, rash, arthralgia, myalgia, hypereosinophilia, acute renal failure)**	**Recommendation**
ASAT or ALAT > 5ULN	No	The treatment should be stopped immediately. **When liver function test return to baseline values**, it may be possible to reintroduce nevirapine on a case by case basis at the starting dose of 200 mg/day for 14 days followed by 400 mg/day. If significant liver function abnormalities rapidly recur, nevirapine must be **permanently discontinued**.
ASAT or ALAT > 2ULN	No	Nevirapine can be continued provided that the patient is closely monitored
	Yes (or signs or laboratory findings of hepatitis)	Nevirapine should be stopped AND NOT READMINISTERED
Unknown	Yes	Liver function testing should be performed

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PROVISIONAL CHANGES INTRODUCED
TO INFORMATION FOR PATIENTS AND PRESCRIBERS

Viramune 200 mg tablets as relevant example

(Changes are underlined)

INFORMATION TO PATIENTS (PACKAGE LEAFLET):

1. BEFORE YOU TAKE VIRAMUNE TABLETS

[List of information necessary before taking the medicinal product]

[Contraindications]

Do not take VIRAMUNE Tablets:

- if you are hypersensitive (allergic) to nevirapine or any of the other ingredients of VIRAMUNE tablets.
- If you previously experienced hepatitis, severe skin rash, abnormalities of the liver function tests associated with clinical symptoms of hypersensitivity or liver injury while on VIRAMUNE treatment.

[Appropriate precautions for use; special warnings]

Take special care with VIRAMUNE Tablets:

The first 8 weeks of treatment with VIRAMUNE are an important period which require a close surveillance to discover the occurrence of severe and life threatening cutaneous reactions and serious hepatic injuries. During this period the dosage of VIRAMUNE prescribed by your doctor must be strictly adhered to, especially during the first 14 days of treatment, so called 'lead-in' period (see more information in *How to take VIRAMUNE*).

Please be sure to inform your doctor if you are suffering from, or have ever suffered from, kidney or liver disease. Also, because VIRAMUNE tablets has been shown to cause variations in liver function, your doctor will monitor the function of your liver by blood tests before and during VIRAMUNE tablets treatment, especially during the first weeks of treatment. If your doctor is worried about the effects of VIRAMUNE tablets on your liver function he or she may decide to perform additional blood tests to monitor the functions of your liver and according to the results he or she may decide to discontinue your treatment. It is important to realise that VIRAMUNE tablets can result in liver toxicity, which in the worst cases can be serious and life-threatening and which has resulted in fatalities (see more information in 'Possible side effects', below).

If you experience clinical symptoms suggesting an injury of the liver, such as loss of appetite, nausea, vomiting, jaundice, you should inform your doctor.

3. HOW TO TAKE VIRAMUNE TABLETS

[Instructions for proper use]
[Dosage]
[Method and/or route(s) of administration]
[Frequency of administration]

It is essential to follow strictly the once a day dosage during the 14-day 'lead in' period before rising to the twice daily dosage.

4. POSSIBLE SIDE EFFECTS

[Description of side effects]

Like all medicines, VIRAMUNE tablets can have side effects.

As mentioned in '*Take special care with VIRAMUNE tablets'*, above, the major side effects of VIRAMUNE tablets are severe and life threatening cutaneous reactions and serious hepatic injuries. These reactions occur mainly in the first 8 weeks of treatment with VIRAMUNE. This is therefore an important period which requires a close surveillance.

If you experience clinical symptoms suggesting an injury of the liver, such as loss of appetite, nausea, vomiting, jaundice, you should inform your doctor.

INFORMATION TO PRESCRIBERS (SUMMARY OF PRODUCT CHARACTERISTICS):

4.2 Posology and method of administration

If patients experience severe rash or a rash accompanied by constitutional findings such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise, nevirapine should be permanently discontinued. Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their nevirapine dose increased until the rash has resolved.

In patients with mild liver function test abnormalities accompanied by signs of hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, nevirapine should be permanently interrupted. Nevirapine should not be restarted in these situations (see section 4.4 Special warnings and special precautions for use).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Nevirapine should not be readministered in case of rapid recurrence of liver function abnormalities in patients who had ASAT or ALAT > 5 ULN during nevirapine therapy, to whom nevirapine had been readministered after liver function tests returned to baseline values.

Nevirapine should not be readministered in patients who had a ASAT or ALAT > 2 ULN associated with hypersensitivity reactions , characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, while on nevirapine therapy.

Nevirapine should not be readministered in patients experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise.

4.4 Special warnings and special precautions for use

On the basis of pharmacodynamic data (see section 5.1) nevirapine should only be used with at least two other antiretroviral agents.

The first 8 weeks of therapy with nevirapine therapy are a critical period which require close monitoring of patients to disclose the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) or serious hepatitis/hepatic failure. In addition the dosage must be strictly adhered to, especially the 14-days lead-in period (see section 4.2 Posology and method of administration).

Cutaneous reactions

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine mainly during the first 8 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity reactions characterised by rash, constitutional findings and visceral involvement. Therefore, patients should be intensively monitored during the first 8 weeks of treatment. Patients should be closely monitored if an isolated rash occurs. Nevirapine must be permanently discontinued in patients developing a serious cutaneous reaction, i.e., Stevens-Johnson syndrome, or toxic epidermal necrolysis (severe rash plus blistering, conjunctivitis, and other findings, such as oral lesions, facial oedema, swelling), or hypersensitivity reaction (characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction). (see section 4.2 Posology and method of administration).

Nevirapine administration above the recommended dose might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Some risk factors for developing serious cutaneous reactions have been identified, they include the lack of respect of the initial dosing of 200 mg daily during the lead-in period and a long time interval between the initial symptoms and the consultation.

Patients should be instructed that the major toxicity of nevirapine is rash. They should be advised to promptly notify their physician of any rash. The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Therefore, patients should be monitored carefully for the appearance of rash during this period. Patients should be instructed that dose escalation is not to occur if any rash occurs during the two-week lead-in dosing period, until the rash resolves.

Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise should discontinue medication and consult a physician. In these patients nevirapine must not be restarted.

Hepatic reactions

Severe and life-threatening hepatoxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. The majority of serious hepatitis and hepatic failure events in nevirapine treated patients that have been reported occurred mainly in the first 8 weeks of therapy.

Patients should be informed that hepatic reactions is a major toxicity of nevirapine demanding a close monitoring during the first 2 months. They should be informed that occurrence of symptoms suggestive of hypersensitivity or hepatitis should lead them to contact promptly their physician.

Liver monitoring

A monitoring of hepatic function should therefore be done every two weeks during the first 2 months of treatment, at the 3rd month and then on a 3-6 monthly basis thereafter. It is also recommended that a liver monitoring should be performed if the patient experiences signs or symptoms suggestive of a hepatitis and/or hypersensitivity reactions.

If ASAT or ALAT > 5 ULN, nevirapine should be immediately stopped. If liver function tests return to baseline values and if there is no signs of hypersensitivity or hepatitis, it may be possible to reintroduce nevirapine, on a case by case basis, at the starting dosage regimen of 200 mg/day for 14 days followed by 400 mg/day. If liver function abnormalities rapidly recur, nevirapine should be permanently discontinued.

If ASAT or ALAT > 2 ULN, then liver tests should be monitored more frequently during regular clinic visits. Physicians and patients should be vigilant for prodomal signs or findings of hepatitis, such as anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness. Patients should be instructed to seek medical attention if these occur.

If ASAT or ALAT > 2 ULN, associated with hypersensitivity reactions characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, nevirapine should be permanently stopped and not be re-introduced.

If clinical hepatitis occurs, characterised by anorexia, nausea, vomiting, icterus AND laboratory findings (such as moderate or severe liver function test abnormalities (excluding GGT)), nevirapine must be permanently stopped and not be re-introduced.

Asymptomatic elevations of liver enzymes are frequently described and are not a contraindication to use nevirapine. Abnormal liver function tests have been reported with nevirapine, some in the first few weeks of therapy. Nevertheless, if patients experience moderate or severe liver function test abnormalities accompanied by hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, nevirapine administration should be permanently interrupted and not re-introduced. Asymptomatic GGT elevations are not a contraindication to continue therapy.

4.8 Undesirable effects

Adults

The postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome and toxic epidermal necrolysis or serious hepatitis/hepatic failure (isolated or associated with other signs of hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction). Most cases have been reported in the first 8 weeks of treatment. This is a critical period which require close monitoring (see section 4.4 Special warnings and special precautions for use).

Skin and subcutaneous tissues

The most common clinical toxicity of nevirapine is rash, with nevirapine attributable rash occurring in 16 % of patients in combination regimens in Phase II/III controlled studies. In these clinical trials 35 % of patients treated with nevirapine experienced rash compared with 19 % of patients treated in control groups of either zidovudine + didanosine or zidovudine alone. Severe or life-threatening skin reactions occurred in 6.6 % of nevirapine-treated patients compared with 1.3 % of patients treated in the control groups. Overall, 7 % of patients discontinued nevirapine due to rash.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Allergic reactions (anaphylaxis, angioedema and urticaria) have been reported. Rashes occur alone or in the context of hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction.

Severe and life-threatening skin reactions have occurred in patients treated with nevirapine, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and hypersensitivity reactions have been reported. The majority of severe rashes occurred within the first 6 weeks of treatment and some required hospitalization, with one patient requiring surgical intervention.

Hepato-biliary

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs), including SGPT, SGOT, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are the most frequent. Cases of jaundice have been reported. Cases of hepatitis (severe and life-threatening hepatoxicity, including fatal fulminant hepatitis) have been reported in patients treated with nevirapine, mainly in the first 8 weeks of treatment. Some of these cases were accompanied by hypersensitivity reactions. This is a critical period which requires close monitoring (see section 4.4 Special warnings and precautions for use).

The most frequently reported adverse events related to nevirapine therapy, across all clinical trials, were rash, nausea, fatigue, fever, headache, somnolence, vomiting, diarrhoea, abdominal pain and myalgia.