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

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EMEA PUBLIC STATEMENT ON LEFLUNOMIDE (ARAVA) - PANCYTOPENIA AND SERIOUS SKIN REACTIONS

The European Commission granted marketing authorisations for the European Union to Hoechst Marion Roussel Deutschland GmbH on 2 September 1999 for the medicinal product Arava, which contains the active substance leflunomide. Arava is not yet marketed in the European Union.

Arava is indicated for the treatment of adult patients with active rheumatoid arthritis as a disease-modifying antirheumatic drug (DMARD). The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP), has been evaluating new safety information as it emerges.

Since September 1998, when Arava was launched in the United States, an estimated 76,100 patients have been treated world-wide. 16 potential cases of pancytopenia (a serious haematological reaction) and 9 cases of serious skin reactions have been reported.

Leflunomide inhibits cellular proliferation. Once administered, it is rapidly converted to an active metabolite (A771726). The elimination of A771726 is slow (i.e. from 1 to 4 weeks are required by the body to eliminate half of this product). Nevertheless, the elimination of this metabolite can be accelerated by the administration of another medicinal product, either cholestyramine or active charcoal (a so-called washout procedure).

The haematological reactions reported with leflunomide may be due to a direct toxicity of the active metabolite of leflunomide while the serious skin reactions may be the consequence of a hypersensitivity reaction to the compound. Furthermore, most of the haematological reactions occurred when leflunomide was administered concomitantly or after treatment with another DMARD or when treatment with leflunomide had just been changed to another DMARD exhibiting an haematological toxicity (e.g. methotrexate).

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

- **Recent treatment with hepatotoxic or haematotoxic DMARDs may result in increased side-effects. Therefore, the balance of risks and benefits has to be carefully considered before treatment with leflunomide is initiated.**
- **Since the active metabolite of leflunomide is slowly eliminated from the organism, serious undesirable effects might occur (e.g. hepatotoxicity, hematotoxicity or allergic reactions) even if the treatment with leflunomide has been stopped. Therefore, when such toxicity occurs or when switching to another DMARD after treatment with leflunomide or in case of desired pregnancy, a washout procedure should be performed.**
- **Considering that the risk associated with combination therapy, in particular in long-term treatment, is unknown and since such therapy can lead to additive or even synergistic toxicity, combination of leflunomide with another DMARD (e.g. methotrexate) is not advisable.**
- **Patients who experience symptoms such as paleness, tiredness, increased proneness to infections, bruising, skin rash or mucous membrane lesions (esp. in the mouth) should contact their doctor immediately.**
- **In the case of a desired pregnancy, patients wishing to become pregnant or father children should inform their doctor beforehand.**

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As an urgent measure, the prescribing and patient information has been modified through a rapid procedure at the request of the marketing authorisation holder. Before the launch of Arava in the European Union, the EMEA thought it necessary to provide this new information to the public.

Relevant changes to the product information (available on the EMEA website since July 1999) are indicated below. For the complete scientific evaluation of Arava and the complete revised product information see the European Public Assessment Report (CPMP/1694/99), also available on the EMEA website.

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PROVISIONAL CHANGES INTRODUCED
TO PRESCRIBING AND PATIENT INFORMATION

INFORMATION TO PATIENTS:

2. BEFORE YOU TAKE ARAVA

Do not take Arava:
if you have ever had an allergic reaction to leflunomide ***(especially a serious skin reaction)*** or to any of the other ingredients (which are listed above under "Other ingredients"),
- ***if you are suffering from a serious infection.***

Take special care with Arava
In certain circumstances (serious side-effects, changing antirheumatic treatment or in case of a desired pregnancy) your doctor will decide that you should take certain medicines which speed up excretion of Arava from your body.

Tell your doctor without any delay if you have symptoms such as paleness, tiredness, increased proneness to infections or bruising. Such symptoms may point to the existence of blood cell disorders which may need discontinuation of Arava and other medications, and further action by your doctor (see also under point 4).

Tell your doctor without any delay if you develop skin rash or mucous membrane lesions (e.g. lesions in the mouth). This is because, in very rare cases, such reactions may develop into severe, sometimes life-threatening bullous skin and mucous membrane reactions. They may, therefore, require discontinuation of Arava and immediate action by your doctor (see also under point 4).

Arava and other medicines for the treatment of rheumatoid arthritis
Combination of leflunomide with other ***medicinal products*** usually given for rheumatoid arthritis [such as antimalarials (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive drugs ***(e.g. methotrexate). is not advisable.***

Other medicines which may interact with Arava
When taking Arava together with medicines which have the potential for causing blood or liver side effects, the possibility of getting such side-effects may be increased (your doctor knows these medicines and will advise you accordingly). This is also true for a while after treatment with Arava has been stopped ***or when such medicines have preceded Arava treatment***.

4. POSSIBLE SIDE-EFFECTS

Occurrence of rash or mucous membrane lesions (e.g. in the mouth) may possibly indicate the development of severe, sometimes life-threatening bullous skin and mucous membrane reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme), which are very rare. Therefore, tell your doctor without any delay if you develop skin rash or mucous membrane lesions. They may require discontinuation of Arava and immediate action by your doctor (see also under point 2).

A decrease in the number of white blood cells (leukopenia) is common, a pronounced decrease is, however, rare, as is an increase in the number of so-called eosinophilic blood cells. A decrease in the number of red blood cells (anaemia) and a decrease in the number of blood platelets (thrombocytopenia) are uncommon. ***A pronounced reduction in the number of all blood cells (pancytopenia) is rare.*** Symptoms such as paleness, tiredness, increased proneness to infections or bruising may point to the existence of such blood cell disorders. ***If such symptoms do occur, inform your doctor at once.***

INFORMATION TO PRESCRIBERS:

4.1 Therapeutic indications

Leflunomide is indicated for the treatment of adult patients with active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD).

Recent treatment with hepatotoxic or haematotoxic DMARDs may result in increased side-effects; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without a washout period may raise the possibility of additive risks of side effects even for a long time after the switching.

4.3 Contra-indications

Arava must not be used in patients with hypersensitivity to leflunomide ***(especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme)*** or to any of the excipients in the tablets.

Leflunomide is contra-indicated in:

- patients with significantly impaired bone marrow function or significant anaemia, leukopenia ***neutropenia*** or thrombocytopenia due to causes other than rheumatoid arthritis,
- patients with ***serious infections***,

4.4 Special warnings and precautions for use

The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. Serious undesirable effects might occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions, see below), even if the treatment with leflunomide has been stopped. Therefore, when such toxicities occur or when switching to another DMARD (e.g. methotrexate) after treatment with leflunomide or in case of a desired pregnancy a washout procedure should be performed.

For the management of the above mentioned toxicities or when switching to another DMARD (e.g. methotrexate) after treatment with leflunomide is indicated, a washout procedure should be performed as detailed below (see required monitoring and washout procedures).

For washout procedures in case of desired pregnancy see section 4.6.

Recommendations for monitoring and washout procedures

Monitoring recommendations
Arava should be administered to patients only under careful medical supervision. AST (SGOT) and ALT (SGPT) as well as blood pressure must be checked before the start of leflunomide treatment and periodically thereafter.

A complete blood cell count, including differential white blood cell count and platelets, must be performed before start of leflunomide treatment as well as every 2 weeks for the first 6 months of treatment, and every 8 weeks thereafter.

Combinations with other treatments
The use of leflunomide with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive agents (with the exception of methotrexate) has not been studied up to now. The risk associated with combination therapy, in particular in long-term treatment, is unknown. Since such therapy can lead to additive or even synergistic toxicity ***(e.g. hepato- or haematotoxicity)***, combination with another DMARD ***(e.g. methotrexate***) is not advisable.

Switching to other treatments
As leflunomide has a long persistence in the body, a switching to another DMARD ***(e.g. methotrexate) without a washout period*** may raise the possibility of additive risks even for a long time after the switching (i.e. kinetic interaction, organ toxicity***).***

Similarly, recent treatment with hepatotoxic or haematotoxic drugs (e.g. methotrexate) may result in increased side-effects; therefore, the initiation of leflunomide treatment has to carefully be considered regarding these benefit/risk aspects***.***

Washout procedure
Cholestyramine 8g is administered 3 times daily. Alternatively, 50 g of activated powdered charcoal is administered 4 times daily. Duration of a complete washout is usually 11 days. The duration may be modified depending on clinical or laboratory variables.

Liver reactions

Since the active metabolite of leflunomide, A771726, is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of A771726 are expected to be increased in patients with hypoproteinaemia or impairment of liver function. Arava is contraindicated in patients with severe hypoproteinaemia or impairment of liver function (see section 4.3).

For persisting ALT (SGPT) elevations of more than 2- to 3-fold the upper limit of normal, leflunomide should be discontinued. Cholestyramine can be administered to more rapidly lower A771726 levels.

Due to a potential for additive hepatotoxic effects, it is recommended that alcohol consumption be avoided during treatment with leflunomide.

Haematological reactions
In patients with pre-existing anaemia, leucopenia, and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of haematological disorders is increased. If such effects occur, a washout (see above) to reduce plasma levels of A771726 should be considered.
In case of severe haematological reactions, including pancytopenia, Arava and any concomitant myelosuppressive medication must be discontinued and a leflunomide washout procedure initiated.

Skin reactions
In case of ulcerative stomatitis, leflunomide administration should be discontinued.
Very rare cases of Stevens Johnson syndrome or toxic epidermal necrolysis have been reported in patients treated with leflunomide. As soon as skin and/or mucosal reactions are observed which raise the suspicion of such severe reactions, Arava and any other possibly associated medicationsmust be discontinued, and a leflunomide washout procedure initiated immediately. A complete washout is essential in such cases In such cases re-exposure to leflunomide is contra-indicated (see section 4.3).

4.8 Undesirable effects

Skin and appendages
Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Haemic and lymphatic system
Common: leukopenia (leukocytes >2 G/l)

Uncommon: anaemia, mild thrombocytopenia (platelets <100 G/l)

Rare: eosinophilia, leukopenia (leukocytes <2 G/l), pancytopenia (probably by antiproliferative mechanism)

Very rare: agranulocytosis

Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological effects.

The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. If a severe undesirable effect of leflunomide occurs, or if for any other reason A771726 needs to be cleared rapidly from the body, the ***washout*** procedure described in section 4.4 has to be followed. ***The procedure may be repeated as clinically necessary. For suspected severe immunological/allergic reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis , a complete washout is essential.***