Specific Safety Information for Prescribers

Leflunomide Bluefish is a ‘disease-modifying antirheumatic drug’ (DMARD) indicated for the treatment of adult patients with active rheumatoid arthritis or active psoriatic arthritis.

As part of the Regulatory authority registration of Leflunomide Bluefish, in the context of the risk management plan of this product, Bluefish Pharmaceuticals has developed this educational program, for physicians who prescribes or will prescribe Leflunomide Bluefish.

This educational material is intended to minimise several risks identified in the frame of the European risk management plan established for Leflunomide Bluefish.

The most important risks you should be aware of when prescribing Leflunomide Bluefish includes:

- Risk of hepatotoxicity, including very rare cases of severe liver injury, which may be fatal
- Risk of hematotoxicity, including rare cases of pancytopenia, leucopenia, eosinophilia and very rare cases of agranulocytosis
- Risks of infections including rare cases of severe uncontrolled infections (sepsis), which may be fatal
- Risk of serious teratogenic effects when administered during pregnancy

Counselling of patients, careful monitoring and following recommendations regarding the wash-out procedure are required to minimise these risks.

Complete prescribing information is provided in the currently approved Summary of Products Characteristics (SmPC), see appendix 2.

COUNSELLING OF PATIENTS

Before starting the treatment with Leflunomide Bluefish, please ensure that patients have been counselled on important risks associated with Leflunomide Bluefish therapy and the appropriate precautions to minimise these risks. A Specific Patient Leaflet has been developed by the Marketing Authorisation Holder in addition to the present safety information sheet.

ROUTINE BLOOD MONITORING

Due to the risk of hepato- and hematoxicity, which in rare cases can be severe or even fatal (see Tables below), a careful monitoring of hepatic parameters and blood cell count before and during treatment with Leflunomide Bluefish is essential.

More information about the occurrence of these adverse drug reactions is available in the attached SmPC.

Concomitant administration of Leflunomide Bluefish and hepatotoxic or hematotoxic DMARDs (e.g. methotrexate) is not advisable, see section 4.4 of the SmPC.

Switching to other treatments:

As leflunomide has a long persistence in the body, a switching to another DMARD (e.g. methotrexate) without performing the washout procedure (see below) 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 hematotoxic medicinal products (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 and closer monitoring is recommended in the initial phase after switching.

LIVER ENZYME MONITORING

LABORATORY TEST	**FREQUENCY**
At minimum ALT (SGPT) must be performed	Before initiating treatment and every 2 weeks during the first 6 months of treatment
	Then, if stable, every 8 weeks thereafter
Confirmed ALT Elevations	**Dose Adjustment/Discontinuation**
Between 2- and 3-fold ULN*	Dose reduction from 20 mg/day to 10 mg/day may allow for continued administration of Leflunomide Bluefish under weekly monitoring
2- to 3-fold ULN persists despite dose reduction -Or- >3-fold ULN is present	Discontinue Leflunomide Bluefish Initiate a wash-out procedure *(see section 'Wash-out procedure')* and monitor the liver enzymes until normalization

* ULN: Upper Limit of Normal

HEMATOLOGIC MONITORING

LABORATORY TEST	**FREQUENCY**
A complete blood cell count, including differential white blood cell count and platelets	Before initiating treatment and every 2 weeks during the first 6 months of treatment
	Then, every 8 weeks thereafter
Discontinuation	
Severe hematologic reactions, including pancytopenia	• Discontinue Leflunomide Bluefish and any concomitant myelosuppressive treatment • Initiate a wash-out procedure (see section 'Wash-out procedure')

INFECTIONS

Leflunomide Bluefish immunosuppressive properties may cause patients to be more susceptible to infections, including opportunistic infections, and may rarely cause severe uncontrolled infections (e.g. sepsis) as well as infections severe in nature, such as Progressive Multifocal Leukoencephalopathy (PML).

Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis.

In the event that severe, uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and administer a wash-out procedure (see section 'Wash-out procedure').

Leflunomide Bluefish is contraindicated in:

Patients with severe immunodeficiency states, e.g. AIDS

Patients with serious infections

PREGNANCY

Please inform the women of childbearing potential, women who wish to become pregnant and men wishing to father a child, about the risk of teratogenic effects with Leflunomide Bluefish and the necessity to use reliable contraception. Please also discuss the measures to follow in case of inadvertent pregnancy during treatment and after treatment's discontinuation. This information should be given before treatment, regularly during treatment and after treatment.

Risk on teratogenic effects

Based on animal studies, the active metabolite of Leflunomide Bluefish, A771726 is suspected to cause serious teratogenic effects when administered during pregnancy. Therefore Leflunomide Bluefish is contraindicated in pregnancy.

WOMEN

STATUS	RECOMMENDATIONS
Women of childbearing potential	Effective contraception required during treatment and up to 2-years after treatment discontinuation
Any delay in onset of menses	Pregnancy testing immediately
Or Any other reason to suspect pregnancy	<u>If confirmed pregnancy:</u> • Discontinue Leflunomide Bluefish • Initiate a wash-out procedure (see below) • Perform A771726 plasma level analysis (see below) • Discuss the risks to the pregnancy with the patient
Women wishing to become pregnant	• Discuss the risks to the pregnancy with the patient, and inform her of the required waiting period of 2 years after treatment discontinuation, before she may become pregnant. If this waiting period under reliable contraception is considered unpractical, prophylactic institution of a wash-out procedure may be advisable. • Initiate the wash-out procedure (see below) • Perform A771726 plasma level analysis (see below)

Wash-out procedure

Start the wash-out procedure (see section 'Wash-out procedure') which allows avoiding the 2-year waiting period. Both colestyramine and activated powdered charcoal are able to modify the absorption of oestrogen and progestrogens, therefore use of alternative contraceptive methods other than oral contraceptives is recommended during the entire wash-out period. If the wash-out procedure cannot be performed, a 2-year waiting period under reliable contraception is required after treatment discontinuation before becoming pregnant.

Testing at the end of the wash-out period

Two separate tests at an interval of at least 14 days must be performed.

- If the 2 test results are < 0.02 mg/L (0.02 µg/mL), no further procedures are necessary. A waiting period of one-and-a-half months between the first result < 0.02 mg/L and fertilization is required.
- If results of either test are > 0.02 mg/L (0.02 µg/mL), the wash-out procedure must be performed again, with 2 separate tests at 14 days of interval.

Between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation, a waiting period of one-and-a-half months is required.

MEN

As there is a possible male-mediated foetal toxicity, reliable contraception during treatment with Leflunomide Bluefish should be guaranteed.

For men wishing to father a child, the same wash-out procedure as recommended for women should be considered.

Between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation, a waiting period of 3 months is required.

MEDICAL INFORMATION SERVICE

An ad-hoc service is available for providing information on leflunomide plasma level testing for patients treated with Leflunomide Bluefish. Please contact Medical Information Services, Bluefish Pharmaceuticals AB to obtain further information +46 (0)8 519 116 00 or drugreaction@bluefishpharma.com.

WASH-OUT PROCEDURE

Plasma levels of the active metabolite of leflunomide, A771726 can be expected to be above 0.02 mg/L for a prolonged period. The concentration may be expected to decrease below 0.02 mg/L about 2 years after stopping the treatment with Leflunomide Bluefish.

The wash-out procedure described in the table below is recommended to accelerate A771726 elimination, when it needs to be rapidly cleared from the body.

<table>
<tr><th>EVENTS WHERE WASH-OUT PROCEDURE IS RECOMMENDED</th><th>WASH-OUT PROCEDURE PROTOCOL</th></tr>
<tr><td>Severe hematologic and hepatic reactions</td><td rowspan="4"><u>After stopping treatment with Leflunomide Bluefish:</u>
• Colestyramine 8 g 3 times daily (24g per day) for 11 days
Colestyramine given orally at a dose of 8 g 3 times a day for 24 hours to 3 healthy volunteers decreased plasma levels of the active metabolite A771726 by approximately 40% in 24 hours and by 49% to 65% in 48 hours.
Or
• 50 g of activated powdered charcoal 4 times daily (200 g per day) for 11 days
Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 g every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the active metabolite A771726 by 37% in 24 hours and by 48% in 48 hours
The duration of the wash-out protocol may be modified depending on clinical or laboratory variables</td></tr>
<tr><td>Severe uncontrolled infections (e.g sepsis)</td></tr>
<tr><td>Pregnancy – planned or not</td></tr>
<tr><td><u>Other events leading to a wash-out procedure:</u>
• Skin and/or mucosal reactions (e.g. ulcerative stomatitis), with suspicion of severe reactions, such as Stevens Johnson syndrome or toxic epidermal necrolysis
• After Leflunomide Bluefish discontinuation and a switch to another DMARD (e.g. methotrexate) which may increase the possibility of additive risk
• For any other reason requiring quick elimination of the active metabolite of Leflunomide Bluefish from the body</td></tr>
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