Direct HealthCare Professional Communication

Beta interferons: risk of thrombotic microangiopathy and nephrotic syndrome

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Dear Healthcare Professional,

The Medicines Authority in agreement with the European Medicines Agency and Biogen Idec Ltd, Bayer Pharma AG, Novartis Europharm Ltd and Merck Serono Europe Ltd would like to inform you of important safety information regarding interferon beta products used in the treatment of multiple sclerosis.

Summary

- **Cases of thrombotic microangiopathy (TMA) including fatal cases, have been reported during treatment of multiple sclerosis with interferon beta products. Most TMA cases presented as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome.**
- **Cases of nephrotic syndrome with different underlying nephropathies have also been reported.**
- **Both TMA and nephrotic syndrome may develop several weeks to several years after starting treatment with interferon beta.**
- **Be vigilant for the development of these conditions and manage them promptly if they occur, in line with the advice below.**

Advice regarding TMA:

- **Clinical features of TMA include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion and paresis) and impaired renal function. If you observe clinical features of TMA, test blood platelet levels, serum lactate dehydrogenase levels and renal function. Also test for red blood cell fragments on a blood film.**
- **If TMA is diagnosed, prompt treatment (considering plasma exchange) is required and immediate discontinuation of interferon beta is recommended.**

Advice regarding nephrotic syndrome:

- **Monitor renal function periodically and be vigilant for early signs or symptoms of nephrotic syndrome such as oedema, proteinuria and impaired renal function especially in patients at high risk of renal disease. If nephrotic syndrome occurs, treat promptly and consider stopping treatment with interferon beta.**

Further information

This communication follows a review by European drug regulatory agencies after reports of TMA and nephrotic syndrome were received in association with use of interferon beta products for the treatment of multiple sclerosis. The review could not rule out a causal association between interferon beta products and nephrotic syndrome or between interferon beta products and TMA.

More information on the conditions:
TMA is a serious condition characterised by occlusive microvascular thrombosis and secondary haemolysis. Early clinical features include thrombocytopenia, new onset hypertension and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) and schistocytes (erythrocyte fragmentation) on a blood film.

Nephrotic syndrome is a nonspecific kidney disorder characterised by proteinuria, impaired renal function and oedema.

The following interferon beta products are authorised for the treatment of multiple sclerosis:

- Avonex®(interferon beta-1a) - Biogen Idec Ltd
- Rebif® (interferon beta 1a) - Merck Serono Europe Ltd
- Betaferon® (interferon beta-1b) - Bayer Pharma AG
- Extavia® (interferon beta-1b) - Novartis Europharm Ltd
- Plegridy®(peginterferon beta-1a) - Biogen Idec Ltd

The Summary of Product Characteristics (SmPCs) and Package Leaflets (PLs) of Avonex, Betaferon, Extavia and Rebif have been updated with information on TMA and nephrotic syndrome **(see Annex).**

The SmPC and PL of Plegridy captured the overall safety information pertaining to the risks of TMA and nephrotic syndrome at the time of granting the marketing authorisation and will be further updated in order to ensure full alignment of the Product Information wording.

Call for reporting

Healthcare professionals should report any suspected adverse reactions or medication errors associated with use of Avonex, Betaferon, Extavia, Rebif and Plegridy, to:

The Medicines Authority or the Marketing Authorisation Holders ;
Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Company contact point
Contact point details for further information or ADR reporting are given in the product information of the medicinal products (SmPC and PL) at: http://www.ema.europa.eu/ema/ or www.maltamedicineslist.com

Post Licensing Directorate
Medicines Authority

Disclaimer
This Direct Healthcare Professional Communication has been submitted to you on behalf of the local representatives of Biogen Idec Ltd, Bayer Pharma AG, Novartis Europharm Ltd and Merck Serono Europe Ltd.

Annex

The following text outlines the updates to the SmPCs for Avonex, Betaferon, Extavia and Rebif. This is not a full SmPC.

Summary of Product Characteristics

4.4 Special warnings and precautions for use

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Thrombotic microangiopathy (TMA)

Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of <product name> is recommended.

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Nephrotic Syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon-beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with <product name> should be considered.

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Section 4.8: Undesirable effects

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Blood and the lymphatic system disorders

Rare: Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome.*

*Class label for interferon beta products (see section 4.4)

Renal and urinary disorders

Rare/uncommon[1]: Nephrotic syndrome, glomerulosclerosis (see section 4.4)

1. Avonex, Plegridy and Rebif: rare; Betaferon and Extavia: uncommon. Frequency classification for each interferon-beta product differs based on different analyses/data.