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Subject: Important safety information on TINTAROS (rosuvastatin)

Dear Health Care Professional,

Actavis Group PTC ehf., in consultation with the Medicines' Authority in Malta would like to emphasize important safety information for Tintaros 5 mg, 10 mg, 20 mg and 40 mg film-coated tablets (rosuvastatin), which is a lipid-lowering agent of the statin class:

Important information:

- **CONTRAINDICATION of the 40 mg once daily dose in patients with predisposing risk factors for myopathy/rhabdomyolysis.**
- **Recommendation that the 40 mg once daily dose be initiated under specialist supervision.**
- **Recommendation that all patients should be started at the recommended starting dose(s) and maintained on the lowest dose that meets their therapeutic goal.**
- **Recommendation of a lower 5 mg once daily starting dose for Asian patients, patients with moderate renal impairment and patients >70 years.**
- **Initiation of therapy with Tintaros 5 mg once daily to be considered for patients requiring less aggressive LDL-C reductions or who have predisposing factors for myopathy.**

Contraindications
See also section 4.3 of the enclosed SmPC.

Tintaros is contraindicated:
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).
- in patients with severe renal impairment (creatinine clearance <30 ml/min).
- in patients with myopathy.
- in patients receiving concomitant ciclosporin.
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- in patients with hypersensitivity to the active substance or to any of the excipients.

The **40 mg dose is contraindicated** in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
- moderate renal impairment (creatinine clearance < 60 ml/min)
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- situations where an increase in rosuvastatin plasma levels may occur
- Asian patients
- concomitant use of fibrates.

Asian patients (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) may be at greater risk of developing muscle related adverse events, including rhabdomyolysis, with rosuvastatin.

Dosing Recommendations
When prescribing Tintaros, all patients should be started at the recommended starting dose and titrated to the lowest effective dose that will meet their individual therapeutic goals.

The recommended starting dose of Tintaros is 5 or 10 mg orally once daily in both statin naïve and patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. A dose adjustment to the next dose level can be made after 4 weeks, if necessary.

In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses, a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed. Specialist supervision is recommended when the 40 mg dose is initiated.

The recommended starting dose for patients with predisposing factors to myophathy, Asian patients, patients with moderate renal impairment (creatinine clearance <60 ml/min) and patients >70 years is 5 mg once daily. For further details on special patient groups, including the paediatric population, see section 4.2 of the enclosed SmPC.

Special warnings and precautions
See also section 4.4 of the enclosed SmPC.

Skeletal muscle effects
Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded and caution should be exercised with their combined use. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40 mg dose.

Liver effects
As with other HMG-CoA reductase inhibitors, rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.
It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.
In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with rosuvastatin.

Renal effects
Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease. The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

The Package Leaflet for Tintaros is intended to:
- Help patients recognize if they have pre-disposing factors for myopathy/rhabdomyolysis.

- Advise those patients who do have pre-disposing factors to discuss these factors with a health care professional before starting treatment with a statin.
- Help patients recognize symptoms of potentially serious adverse events (myalgia, myopathy and rhabdomyolysis) for which timely consultation with a health care professional is advised.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions of a medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse reaction can also be reported to the Medicines Authority. 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, Gzira GZR 1368, Malta, or sent by email to postlicensing.medicinesauthority@gov.mt

If you have any questions regarding this information, please contact Actavis via email on phv@actavis.com.mt, by phone on +356 22483330 or by post to Actavis Marketing & Sales Offices, Tarxien Road, TXN 1095, Malta.

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