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

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PUBLIC STATEMENT ON
TROVAN / TROVAN IV / TURVEL / TURVEL IV (Trovafloxacin/Alatrofloxacin)

SERIOUS, SEVERE AND UNPREDICTABLE LIVER INJURIES

The European Commission granted marketing authorisations for the whole European Union to Pfizer Limited on 3 July 1998 for TROVAN (trovafloxacin) and TROVAN IV (alatrofloxacin) and to Roerig Farmaceutici Italiana S.p.A. on 8 July 1998 for TURVEL (trovafloxacin) and on 3 July 1998 for TURVEL IV (alatrofloxacin). TROVAN/ TROVAN IV is currently marketed in eight member states of the European Union (Austria, Denmark, Finland, Germany, Netherlands, Portugal, Spain and Sweden). TROVAN is available as 100 mg and 200 mg film coated tablets, and TROVAN IV 5 mg/ml concentrate for solution for infusion (20, 40 and 60 ml vials). Only TURVEL is currently marketed in the European Union in one member state, Spain and available as 200 mg film coated tablets. The indications are detailed below.

An estimated number of 2,500,000 prescriptions have been made world wide for trovafloxacin/ alatrofloxacin including approximately 200,000 prescriptions in Europe since the first authorisation (USA, December 1997). Since the introduction of trovafloxacin/ alatrofloxacin in Europe the Scientific Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA), has been evaluating new safety information as it emerges.

The marketing authorisation holders informed the EMEA in May 1999 concerning new information on serious and severe liver events. Since February 1998, 140 documented cases of serious hepatic events have been reported. The serious adverse reactions include eight spontaneous cases (including four cases of hepatic necrosis) where patients died or required a liver transplant. The review of these cases shows that in 35 % of cases the reported liver/biliary events were accompanied by a hypersensitivity reaction. In addition, the occurrence of the liver injuries varied between 1 – 60 days after start of the treatment. These data suggest that the onset and the severity of these liver injuries are **unpredictable**. In the light of this new information, the CPMP has started to reassess the risk/benefit balance of these products.

- **Following an initial review, the CPMP wishes to inform patients and prescribers as to the unpredictability and potential severity of liver injuries. The expected benefit of the treatment has to be assessed on a case by case basis by the prescribing physician in the context of this new information.**
- **The current patient information leaflet already states that, patients should be informed to immediately stop the treatment and consult their doctor if they develop symptoms suggestive of a hypersensitivity reaction (skin rash, hives, face oedema, arthralgia, etc).**
- **The risk of re-exposure of the product to patients should be assessed on a case by case basis because of the possible immuno allergic nature of the effect.**
- **In addition, patients should be informed to immediately stop the treatment and consult their doctor if they develop signs and symptoms suggestive of liver or pancreatic injury (fatigue, anorexia, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine).**

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Although the information available to date is preliminary, the marketing authorisation holders requested on 19 May 1999 the introduction, through a rapid procedure, of provisional changes to prescribing and patient information. The revised relevant parts of this information are indicated below. This procedure has been completed and marketing authorisation holders have informed the EMEA that it is communicating these changes to prescribers through a "Dear Doctor letter".

TROVAN IV / TURVEL IV is currently authorised for the intravenous treatment of community acquired pneumonia and nosocomial pneumonia (mild, moderate and severe), complicated intra-abdominal infections and acute pelvic infections, complicated skin and soft tissue infections. TROVAN / TURVEL is currently authorised for the oral treatment of community acquired pneumonia and nosocomial pneumonia (mild, moderate and severe), acute exacerbations of chronic bronchitis, acute sinusitis, complicated intra-abdominal infections and acute pelvic infections, salpingitis, uncomplicated gonococcal urethritis and cervicitis, and chlamydial cervicitis and complicated skin and soft tissue infections.

The EMEA will continue to review all new safety information relating to this issue and will take all adequate regulatory steps as appropriate.

Prof Rolf Bass
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Information for Patients (example for TROVAN tablets)

PRECAUTIONS FOR USE

Inform your doctor if you have been previously treated with TROVAN/ TROVAN IV.

SPECIAL WARNINGS

Very rarely inflammation of the liver or pancreas has been seen in patients receiving TROVAN. If you develop symptoms such as fatigue, anorexia, yellowing of the skin and eyes, severe upper stomach pain with nausea and vomiting, or dark urine, you should stop taking this medication and see your doctor immediately.

Information for Prescribers (example for TROVAN tablets)

4.2 Posology

- ***In view of the possible risks of hypersensitivity and hepatitis (see sections 4.3 and 4.4) careful consideration should be given to the risks and benefits of treatment before patients previously treated with Trovafloxacin/ Alatrofloxacin are re-exposed to the product.***

4.4 Special warnings and special precautions for use

- ***During the post-marketing period, very rare cases of serious hepatic adverse events have been reported. Many of these cases have been associated with serious underlying diseases and/or concomitant medications that may have contributed to the clinical picture. Some of these events may occur unpredictably, having no obvious associated risk factors such as dose or duration of therapy. Trovan-related hepatotoxicity is generally reversible on discontinuation of therapy; however, liver failure, resulting in liver transplant and/or death, has been reported very rarely. Trovan should be discontinued immediately if clinical signs and symptoms consistent with liver dysfunction develop.***
- ***The safety of trovafloxacin has only been established for the recommended dosage regimens. Prolonged use or use of higher doses than recommended may be associated with increased adverse events. In a comparative study where oral trovafloxacin was administered for 28 days a higher incidence of liver enzyme elevations was noted on trovafloxacin. These abnormalities mostly resolved during the 10 week follow-up after the medicinal product was discontinued.***
- ***Allergic reactions including anaphylaxis have been reported very rarely with trovafloxacin. In the event of an allergic reaction, treatment with trovafloxacin should be discontinued immediately and adequate supportive procedures initiated.(See section 4.8)***
- ***Pancreatitis has been reported very rarely. Patients developing symptoms consistent with pancreatitis should discontinue treatment immediately and should be monitored appropriately***

4.8 Undesirable effects

HEPATOBILIARY

Rare	***hepatitis (including acute hepatic necrosis).***
Very rare	***liver failure (resulting in some cases in liver transplant and/or death).***