



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

London, 15 June 1999
EMEA/18046/99

**PUBLIC STATEMENT ON
TROVAN / TROVAN IV / TURVEL / TURVEL IV (Trovfloxacin/Alatrofloxacin)
RECOMMENDATION TO SUSPEND THE MARKETING AUTHORISATION IN THE
EUROPEAN UNION**

The European Commission granted marketing authorisations for the whole European Union to Pfizer Limited on 3 July 1998 for TROVAN (trovfloxacin) and TROVAN IV (alatrofloxacin) and to Roerig Farmaceutici Italiana S.p.A. on 8 July 1998 for TURVEL (trovfloxacin) and on 3 July 1998 for TURVEL IV (alatrofloxacin).

The scientific Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA), during its extraordinary meeting on 10 June 1999, adopted an Opinion recommending the suspension of the marketing authorisation of TROVAN/TROVAN IV and TURVEL/TURVEL IV. This was due to increasing concerns over 152 documented reports of serious hepatic events, including 9 cases where patients died or required a liver transplant. The background to this procedure and the grounds for the suspension are provided in Annex 1.

Following the CPMP meeting on 19 May 1999, as a precautionary measure, the CPMP had already alerted health care professionals to the occurrence of serious, severe and unpredictable liver injuries associated with trovfloxacin/alatrofloxacin administration. The CPMP had also decided to re-assess the risk/benefit profile of the medicinal products containing trovfloxacin/alatrofloxacin (see Public Statement on TROVAN/ TROVAN IV/ TURVEL/ TURVEL IV No EMEA/15770/99 dated 25 May 1999).

TROVAN¹/ TROVAN IV² is currently marketed in eight member states of the European Union (Austria, Denmark, Finland, Germany, Netherlands, Portugal, Spain and Sweden). TURVEL³ is currently marketed in the European Union in only one Member State, Spain.

The above mentioned Opinions have been forwarded to the marketing authorisation holders, the Member States, and the European Commission. The European Commission has initiated the decision-making procedure relating to the suspension of the marketing authorisations. The Commission has notified the competent authorities of the Member States that the process has started and recommended that they suspend the use of TROVAN/ TURVEL and TROVAN IV/ TURVEL IV. Existing supplies of TROVAN/ TURVEL and TROVAN IV/ TURVEL IV will consequently be withdrawn from pharmacies and wholesalers.

¹ TROVAN is available as 100 mg and 200 mg film coated tablets

² TROVAN IV is available as 5 mg/ml concentrate for solution for infusion (20, 40 and 60 ml vials)

³ TURVEL is available as 200 mg film coated tablets

Information to patients:

Patients currently using TROVAN/ TURVEL should contact their physician to review their treatment. Patients should not stop taking TROVAN/ TURVEL until their physician has recommended that they do so.

Information to prescribers:

Physicians should not issue any new prescription of TROVAN/ TROVAN IV/ TURVEL/ TURVEL IV and should review treatment of patients currently under TROVAN/ TROVAN IV/ TURVEL/ TURVEL IV (e.g. switching to alternative antibiotics, discontinuation of treatment).

The EMEA will continue to review all new information relating to this issue and will take all adequate regulatory steps as appropriate. Details of the marketing authorisation holders and their local representatives are provided in Annex 2.

Prof Rolf Bass
Head of Human Medicines Evaluation Unit
Tel: +44-171-418 8411

cont/....

**Background and Grounds for Opinion Suspending the Marketing Authorisations of
TROVAN/ TURVEL/ TROVAN IV/ TURVEL IV**

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 IV / TURVEL IV are currently authorised for the intravenous treatment of community acquired pneumonia and nosocomial¹ pneumonia (mild, moderate and severe), complicated intra-abdominal infections and acute pelvic infections, complicated skin and soft tissue infections. TROVAN / TURVEL are 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, salpingitis² uncomplicated gonococcal urethritis and cervicitis², and chlamydial cervicitis and complicated skin and soft tissue infections.

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).

Between February 1998 and 6 May 1999, 140 documented cases of serious hepatic events have been reported. The serious adverse reactions include eight spontaneous cases (including four cases of hepatic necrosis³) 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.

On the basis of this information, the marketing authorisation holders, requested on 19 May 1999 the introduction, through urgent safety restrictions, of provisional changes to prescribing and patient information, to inform patients and physicians as to the unpredictability and potential severity of liver injuries. The risk of re-exposure of the products to patients was required to be assessed on a case by case basis because of the possible immuno allergic nature of the effect. In addition, it was recommended that trovafloxacin/ alatrofloxacin be discontinued, immediately if clinical signs and symptoms consistent with liver dysfunction developed.

In the period between 6 to 21 May 1999, 12 further cases of severe hepatic events in patients treated with trovafloxacin/ alatrofloxacin were reported to the EMEA, one of them leading to a liver transplant.

On 10 June 1999, the Pharmacovigilance Working Party re-evaluated the safety profile of trovafloxacin/ alatrofloxacin. In addition, an ad-hoc expert group re-evaluated the efficacy of trovafloxacin/ alatrofloxacin in the authorised indications and considered the therapeutic place of the product as compared to other antibiotics. Conclusions of both meetings were presented to an extraordinary CPMP meeting on the same day.

The CPMP concluded, that there is a clear causal association between the use of trovafloxacin/ alatrofloxacin and serious hepatic adverse reactions (e.g. acute hepatic failure leading to liver transplants or death). Comparative US spontaneous reporting data provide a strong signal that such reactions are notably more frequent and more severe with trovafloxacin/ alatrofloxacin as compared to other quinolones and other antibiotics.

¹ refers to an hospital acquired infection

² gynaecological infections

³ destruction of liver cells

The occurrence of serious and severe hepatic injuries, associated with trovafloxacin/ alatrofloxacin is unpredictable and no preventive measures have been identified. This risk of hepatotoxicity constitutes an unacceptable hazard if not balanced by a high beneficial therapeutic effect as compared to existing antibiotics.

During the course of the extraordinary CPMP meeting the marketing authorisation holders made an oral presentation with respect to potential advantages of trovafloxacin/ alatrofloxacin as compared to other antibiotics. This included the availability of oral and IV form, its intrinsic antibacterial activity (in vitro) in particular its broad spectrum of activity facilitating empiric therapy, specific activity against penicillin resistant *Streptococcus pneumoniae* and against anaerobes and its therapeutic potency as a single drug in place of combination therapy.

In addition, the marketing authorisation holders proposed to limit the indications in the European Union to the treatment of patients who meet all of the following criteria:

- Patients who have at least one of the following five types of serious and life or limb threatening infections that is judged serious and life or limb threatening by the treating physician: nosocomial pneumonia, community acquired pneumonia, complicated intra-abdominal infections, acute pelvic infections and complicated skin and soft tissue infections.
- Patients who begin their treatment as an inpatient in hospital.
- The treating physician believes that, given the new safety information, the benefit of the product for the patient still outweighs the potential risk.

The clinical database presented in the original Marketing Authorisation Applications was reviewed by the Committee to identify any evidence of a superior clinical efficacy with respect to the comparator agents used. The results of this review indicated that no clinically significant superiority of trovafloxacin/ alatrofloxacin relative to the comparators had been demonstrated. The studies were performed in patients with mild to severe infections.

Efficacy in patients with very severe nosocomial pneumonia and in particular infections due to less susceptible pathogens e.g. *Pseudomonas aeruginosa*, has not been established.

Therefore, the CPMP concluded that even for the proposed restricted indications suitable therapeutic alternatives exist.

The CPMP proceeded to discuss whether there were some “niche” indications⁴ for trovafloxacin/ alatrofloxacin relating to potential advantages due to the treatment of severe infections, exceptional activity against specific pathogens and use in patients allergic to beta lactam antibiotics. Considering the availability of existing alternatives, the evidence available on the use of trovafloxacin/ alatrofloxacin did not allow the identification of such a “niche” indication where the benefit would outweigh the known and unpredictable occurrence of serious hepatic injuries associated with the use of trovafloxacin/ alatrofloxacin.

Conclusion: It was not possible to identify any indication where the therapeutic benefit would outweigh the occurrence of severe, serious and unpredictable hepatic injuries associated with the use of trovafloxacin/ alatrofloxacin.

Following review of the new safety data and reassessment of the safety and efficacy profile of trovafloxacin/ alatrofloxacin, the CPMP considered that the risk/benefit ratio of TROVAN/ TURVEL/ TROVAN IV/TURVEL IV is now negative and the Committee recommended, by consensus, to suspend the marketing authorisations of these medicinal products.

⁴ limited indications for which no therapeutic alternatives exist
EMEA/18046/99

GROUNDINGS FOR SUSPENSION OF THE MARKETING AUTHORISATIONS

Whereas, the CPMP is of the Opinion that TROVAN/ TURVEL/ TROVAN IV/ TURVEL IV can no longer be safely maintained in normal clinical usage for the following reasons:

- severe, serious and unpredictable hepatic injuries
- taking into consideration this hepatotoxicity, the overall benefit/ risk balance of trovafloxacin/ alatrofloxacin was considered to be unfavourable in the authorised indications and it was not felt possible to restrict the indications adequately to permit safe use

the CPMP has recommended the suspension of the marketing authorisations for TROVAN/ TURVEL/ TROVAN IV/TURVEL IV.

Details of the Marketing Authorisation Holders and their local representatives**Marketing Authorisation Holders****Trovan/ Trovan IV:**

Pfizer Limited, Ramsgate Rd., Sandwich, Kent CT13 9NJ, United Kingdom.
Tel: +44 (0)1304 61 61 61

Turvel/ Turvel IV:

Roerig Farmaceutici Italiana S.p.A., S.S. 156 - Km 50, 04010 Borgo San Michele, (Latina), Italy.
Tel: +39 (0)633 18 23 09

Local Representatives**Belgique / België /Belgien**

Pfizer S.A.
Rue Léon Theodor 102
B-1090 Bruxelles / Brussel
☎ +32 (0)2 421 15 11

España

Pfizer S.A.
Avenida de Europa 20-B
Park Empresarial La Moraleja
E-28108 Alcobendas (Madrid)
☎ +34 (91) 490 97 79

Italia

Pfizer Italiana S.p.A.
Via Valbondione, 113

I-00188 Roma

☎ +39 (0)6 33 18 21

Nederland

Pfizer BV
Postbus 37
NL-2900 AA Capelle aan den
IJssel
☎ +31 (0)10 406 42 00

Suomi / Finland

Pfizer Oy
Lars Sonckin kaari 4
FI-02600 Espoo

☎ +358 (0)9 43 00 40

Danmark

Pfizer A/S
Lautrupvang 8
DK-2750 Ballerup
☎ +45 44 20 11 00

France

Pfizer S.A.
86, rue de Paris
F-91407 Orsay Cedex

☎ +33 (0)1 69 18 66 66

Republic of Ireland

Pfizer (Ireland) Limited
Parkway House
Ballymount Road Lower
IRL-Dublin 12

☎ +353 1800 633 363

Österreich

Pfizer Corporation Austria
Ges.m.b.H.
Seidengasse 33-35
A-1070 Wien
☎ +43 (0)1 521 15-0

Sverige

Pfizer AB
Box 501
SE-183 25 TÄBY

☎ +46 (0)8 519 062 00

Deutschland

Pfizer GmbH
Pfizerstraße 1
D-76139 Karlsruhe
☎ +49 (0)721 61 01 01

Ελλάδα

Pfizer Hellas A.E.
Γραφείο
GR-116 33 Αθήνα

☎ +30 (0)1 7517981

Luxembourg

Pfizer S.A.
Rue Léon Theodor 102

B-1090 Bruxelles/Brussel
Belgique
☎ +32 (0)2 421 15 11

Portugal

Laboratórios Pfizer, Lda.
Apartado 30
P-2830 Coima

☎ +351 (0)1 227 8200

United Kingdom

Pfizer Limited
Ramsgate Rd
Sandwich, Kent
GB-CT13 9NJ
☎ +44 (0)1304 61 61 61