The European Agency for the Evaluation of Medicinal Products
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 July 2003
CPMP/19335/03/Rev-1

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS SUMMARY OF OPINION*
for
YONDELIS

International Nonproprietary Name (INN): **t**rabectedin

On 24 July 2003 the Committee for Proprietary Medicinal Products (CPMP) adopted a negative opinion,** recommending not to grant a marketing authorisation for the medicinal product Yondelis, 0.25 mg and 1 mg, powder for concentrate for solution for infusion intended for patients with advanced soft tissue sarcoma (STS), having failed anthracyclines and ifosfamide, or having failed ifosfamide and unsuitable to receive anthracyclines.

Yondelis was designated as an orphan medicinal product on 30 May 2001 (EU/3/01/039). The applicant for this medicinal product is Pharma Mar S.A.

The active substance of Yondelis is trabectedin, a new anti-cancer medicinal product (antineoplastic agent - L01CX01). Trabectedin mechanism of action is to block the transcriptional activation of a subset of inducible genes without affecting their constitutive expression.

The grounds for the negative opinion relate to the following points:

- The CPMP found that the anti-tumour activity of trabectedin in the treatment of double-resistant STS could not be considered outstanding. In the absence of outstanding activity, efficacy cannot be established outside randomised trials,
- The sub-population for the efficacy evaluation and the historical control were identified retrospectively; the absence of pre-specification as regards key measures and comparisons violates fundamental methodological principles and may introduce bias in the assessment of benefit/risk balance,
- Time to progression (TTP) on last prior therapy before inclusion in the trabectedin studies was found to be twice as long as TTP on trabectedin therapy. In contrast, progression free survival (PFS) on trabectedin was found to be very similar to PFS on ifosfamide second-line in the historical comparison. Despite similarity in PFS in the historical comparison overall survival data appeared to favour trabectedin at late time points. Altogether these partly contradictory findings indicate that the historical comparison with ifosfamide is hampered by bias,
- The wide confidence intervals around the point estimates for objective tumour response rate (RR) and PFS at 6 months, the trends towards even lower anti-tumour activity in the French ATU[1] programme and the possible non-representativeness of patients included in the retrospective evaluation of efficacy, altogether seriously question the possibility to estimate with reasonable certainty the anti-tumour activity of trabectedin for patients in clinical practice,
- Efficacy cannot be established based on a modest and currently rather ill-defined anti-tumour activity in a disease where the predictive value of these measures (RR and PFS) can be questioned for endpoints of immediate relevance to the patient,

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* Summaries of opinion are published without prejudice to the Commission Decision, which will normally be issued within 90 days from adoption of the Opinion.

** Applicants may appeal any CPMP opinion, provided they notify the EMEA in writing of their intention to appeal within 15 days of receipt of the opinion.

1 Authorisation Temporaire d' Utilisation (Scheme for compassionate use implemented in France)

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 8613
E-mail: mail@emea.eu.int http://www.emea.eu.int

- In the absence of unequivocally proven efficacy, the manageable but significant toxicity profile of trabectedin constitutes a concern.

The CPMP, on the basis of quality, safety and efficacy data submitted, considers that benefit to risk balance for Yondelis was not demonstrated to be favourable and therefore cannot recommend the granting of the marketing authorisation.