

**SURVEY ON WARNING SYSTEMS FOR MEDICINAL DRUGS  
AFFECTING DRIVING PERFORMANCE**

**DGC 98-02**

**Study conducted with support of  
the Directorate General for Transport of  
the Commission of the European Communities and  
the Belgian State Secretary for Security**

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**October 1998**

01N-0397

TS13

Descriptions of methodology of experimental research on drugs affecting driving performance are still poorly indicated, although descriptive information exists based on the consensus of scientific opinion.

Some harmonization has been achieved, for example in the provision of a specific Note for Guidance on the Summary of Product Characteristics of benzodiazepines as anxiolytics. The recommended information for the warning concerning the effects on ability to drive and use machines is standardized and offers no opportunity of distinguishing between various benzodiazepines if proof of different behavioural toxicity exists based on experimental and/or pharmaco-epidemiological research. Unfortunately, this situation has not been recognised by the drug regulatory authorities as an obstacle to categorizing. Hence it is recommended that a better structure of guidelines be set up to assist drug manufacturers in applying drug testing methodologies which do allow categorization and to reconsider the use of standard information for the warning section in the Summary of Product Characteristics.

- *Failure to categorize*: a major problem when categorizing drugs will be the lack of support from those who have to submit the relevant data, i.e. the drug manufacturers. Even if a standardized methodology has been applied in testing the drug's impairing properties, there will always be discussion with drug companies as to whether their drugs, belonging to the same therapeutic class, have to be assigned to different categories. Categorization will only satisfy the needs of the drug manufacturers if their drugs can be distinguished as 'safer' than the competitors' drug. Some drug regulatory authorities indicated that experimental research alone is not convincing enough to formulate different warnings. They suggested that revision of the warning system should be based on results obtained

in large populations who have used the drugs, and by allowing the investigators to assess the risk potential of accident involvement for the individual drugs. It is unclear whether there will be a need for the European Medicines Evaluation Agency (EMA) to provide specific expertise in this area. EMA is not only responsible for international harmonization in the approval of pharmaceutical products, but also for coordination of national activities in the area of post-marketing surveillance to ensure the safety of medicinal products circulating within the Community. Although most regulatory authorities feel much more comfortable in selecting their own experts, some of them would welcome specific expertise provided by EMA. It is recommended that EMA starts an investigation to decide whether or not it should coordinate large-scale, case controlled pharmacoepidemiological surveys based upon existing data-bases in different Member States to determine the relative risks of traffic accidents for users of all drugs identified as potentially dangerous.

- *Examples of warnings in the Summary of Product Characteristics* : it is an exception if the statement in the driving warning is explicit. For example in Finland the driving warning for buspirone (an anxiolytic) is clear: 'Does not affect driving...'. Most examples of driving warnings provided by the different regulatory authorities in this survey are vague, illogical and sometimes misleading. In general the pattern of information is the following: it starts with a list of side effects affecting the central nervous system, then it states that these effects may impair mental and/or physical abilities required for the performance of potentially hazardous tasks. It ends with the advice that patients should be told to use caution in such activities until their individual responses to the drug have been well-established. How to act or to look for individual susceptibility before driving or

operating machinery remains a 'secret'. It would be advisable to investigate the impact of present driving warnings in package inserts on physician's attitudes towards instructing their patients who drive or operate machines, and on patients' intentions and attitudes towards changing their drug-taking and driving behavior in the different Member States. The results will constitute adequate feedback to drug regulatory authorities and drug companies who are responsible for providing the warnings.

- *Opportunities to improve warnings:* a slight majority of respondents believe that a warning symbol based on a categorization system could improve the effectiveness of warnings provided as long lists of side effects. One opportunity to improve the readability of the label and package inserts by developing specific guidelines for certain categories of medicinal drugs has been foreseen in the new European Guideline on this subject (III/5218/97, final approval September 1998). Clear statements are prescribed and pictograms may be used as an additional measure if they make the message clearer to the patient. There are movements towards categorization systems for improving warnings in at least three Member States: Belgium, Germany and the Netherlands. It is obvious that these initiatives will have an impact on the views of patients, physicians and pharmacists pertaining to improved warning systems for patients who drive or operate machines. It would be advisable to act in accordance with present European Directives and Guidelines aiming at improving the readability of labels and package inserts. Warning symbols based on categorization are feasible and are based on scientific consensus. By investigating the acceptance of a new warning symbol among patients, health care providers and drug manufacturers, drug regulatory authorities could be more proactive as a response to the actual needs of those who use the

information presented in the package inserts.

Table 1. Examples of discrepancies in driving warnings in different Member States.

Drug (indication)	EU Member State	Driving warning in the SPC
Citalopram (Anti-Depressant)	Spain	Does not impair..... However, patients should be cautioned.....
	United Kingdom	Does not impair..... However, some impairment expected....
	Belgium	Does not impair..... Does not potentiate alcohol effects...
	France	Does not show impairment but may affect skills.....
	Netherlands	May impair..... Patients should be cautioned.....
Piracetam (Nootropic)	Finland	Some patients may experience drowsiness.... Caution advised for.....
	Belgium	(No data provided in the SPC)
	United Kingdom	No experience on driving ..... Caution should be exercised.....
Topiramate (Anti-Epileptic)	France	(Long list of side effects).... Patients should be warned....
	Finland	May impede motor skills....
	United Kingdom	Drowsiness is likely to occur.... More sedating than other anti-epileptic drugs.... Could be potentially dangerous....
	Belgium	Drowsiness and dizziness are minor side effects.... But patients should be warned...
Lamotrigine (Anti-Epileptic)	Netherlands	Due to CNS effects patients should be cautious....
	Finland	Because of individual response patient has to consult his doctor....
Nefazodone (Anti-Depressant)	United Kingdom	Modest to no impairment.... However, patients should be cautioned...
	Finland	Take into account that the ability to react will slow down...
Reboxetine (Anti-Depressant)	Germany	Does not impair..... However, patients should be cautioned...
	Finland	Patients must be warned about effects on driving...
Buspirone (Anxiolytic)	Spain	Patients should be warned about effects and advised not to drive...
	Finland	Does not affect driving....