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Establishment of Criteria for a European Categorisation System for Medicines and Driving

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Task 4.2.

Establishment of Criteria for a European Categorisation System for Medicines and Driving

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ADR: Adverse Drug Reaction

AFSSAPS: Agence Française de Sécurité Sanitaire des Produits de Santé (French Health Products Safety Agency)

ATC: Anatomical Therapeutic Chemical classification system

BAC: Blood Alcohol Concentration

CERMT: Centre d'Etudes et de Recherches en Médecine du Trafic

CHMP: Committee for Medicinal Products for Human Use

CMD (h): Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

DG MOVE: Directorate General for Mobility and Transport

DG SANCO: Directorate General for Health and Consumers

DG TREN: Directorate General for Energy and Transport

DGT: Dirección General De Tráfico (Traffic General Directorate)

DRUID: Driving Under the Influence of Drugs, Alcohol and Medicines

EC: European Commission

EMA: European Medicines Agency

EU: European Union

ICADTS: International Council on Alcohol, Drugs and Traffic Safety

PIL: Patient Information Leaflet

SemFyc: Sociedad Española de Medicina de Familia y Comunitaria (Spanish Association of General Practitioners)

SmPC: Summary of Product Characteristics

UVa: University of Valladolid

WP: Work Package

Executive Summary

The aim of this deliverable is to develop and agree on input for the establishment of a European categorisation system for medicines and driving. After a short review of the most significant existing developments of categorisation systems in Europe, a discussion has been presented to explain the need for such a categorisation system. It is clear that such a system will serve most of the needs of health care professionals, drug regulatory agencies, drug manufacturers and patients. For patients to make the best (and safest) use of their medicines, clear warnings are needed. The development of a multi-level categorisation system in France was examined with respect to identifying difference between the least and most impairing medicine within one therapeutic class, and the utilisation of warning labels to guide patients decisions about driving and taking medicine.

For the development of input for a European categorisation system it was decided to address the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP). Together with WP 4 Partners three small-scale invitational workshops were organised in 2008 in which representatives of regulatory agencies in 9 Member States participated. Based on their discussions, it was highlighted that any developed categorisation system should be in line with the Guideline for the Summary of Product Characteristics (SmPC). Subsequently, through a consultation process, the SmPC was amended and adopted in September 2009 to achieve a greater differentiation of descriptions of levels of influence as a) no or negligible influence, b) minor, c) moderate influence, and d) major influence on driving fitness, with some important guidance in special circumstances.

In describing the various categories, discussions among WP 4 partners clearly showed that emphasis should be given to the evaluation of the active substances in order to increase the feasibility of such a system. In order to categorise a medicine with regard to driving, several steps are identified using data from different sources: pharmacodynamic and pharmacokinetic data; pharmaco-vigilance data, experimental and epidemiological data and additional data (e.g.

from the study of accidents). In addition, for each category information for developing directions for health care professionals and warnings for patients could be presented. However, important differences were highlighted between countries over the use of symbols.

In the last two years (2010 and 2011) of Task 4.2, progress and steps forward based on the input from WP4 partners have been discussed with the Pharmacovigilance Working Party, resulting in a consensus development based on a common approach. Currently national approaches differ substantially: from France at one end of the spectrum (with three-level pictogram labelling) to Sweden at the other end where the existing pictogram was replaced with a generic warning in the patient leaflet. Consensus was reached that a basic 2 level framework would be developed as the basis for warnings to the patient in the Patient Information Leaflet. For medicines without a potential relevant influence on driving (no or negligible, or minor influence) and for medicines with a potential relevant influence on driving (moderate influence, or major influence), warnings for the patient have been proposed.

This consensus on the wording in the Patient Information Leaflet is an important step to harmonize information to patients on the potential for a medicine's impairing effects on fitness to drive. However, it is acknowledged by the Pharmaco-vigilance Working Party and WP4 partners that at the Member States' level further discretionary activities may be undertaken in order to reinforce the awareness of patients on the effects of medicines on fitness to drive.

In the recommendations of this Deliverable emphasis is given to improve information related to effects on driving in the Patient Information Leaflet by simple and patient-centred directions. The 2 level system for the Patient Information Leaflet should be further based on clarifying the criteria for the evidence in forming the categories. Therefore collaborative efforts by DRUID experts, and the members of the Pharmacovigilance Working Party, among other bodies, preferably with support of EU bodies, such as DG Sanco and DG Move, are recommended. Finally it is recommended, that the development of supplementary information for patients (e.g. warning levels and pictograms) and health care professionals (e.g. prescribing and dispensing guidelines) should be

guided with input provided by DRUID results (D4.2.1, D 4.3.1, D 7.3.2 and D 7.4.2.) as well as experience in EU Member States.

Introduction

Historical perspective

Within the sixth Framework Programme the DRUID-project (Driving Under the Influence of Drugs, Alcohol and Medicines, FP6-518404) started as an Integrated Project in October 2006. DRUID aims to combat the scourge of drink-driving and find solutions to the issue of the use of drugs and medicines. It will bring together the most experienced organisations in Europe to assemble a coordinated set of data, resources and measures. The consortium is comprised of a total of 37 institutes from 19 States (18 EC Member States and Norway).

European policy development

Over 40,000 people were killed and around 1.7 million suffered from some kind of injury on the roads in the year 2000 in the EU (15 Member States). The EU has fixed the target date of 2010 to reduce the number of fatalities by 50% (White Paper) [1]. In the European Union, as well as in many other parts of the world, such as the USA, Canada, and Australia, specific regulations exist concerning fitness to drive, including rules to review the use of medicinal drugs [2-5]. A recent European Union Council Resolution highlighted the need to combat the impact of psychoactive substance use on road accidents [6].

Within the European Union a Report on Drugs, Medicines and Driving was adopted by DG TREN (Directorate General for Energy and Transport) Working Group on Alcohol, Drugs and Medicines and Driving, which presented the following recommendations [7]:

1. To undertake further research to establish the prevalence and role of medicinal drugs in road accidents.

2. To develop common guidelines about the information given to patients by

practitioners and pharmacists.

3. To inform users with appropriate and harmonised labelling or pictograms on medicine packages.

4. To implement a Europe-wide classification of medicinal drugs, based on:
    a) the pharmacological effects of the drugs;
    b) their therapeutic indications with regard to the different categories of driving licences and the decisions of the medical authorities for driving licences.

5. To adapt driving licence requirements in order to permit allowances or restrictions for drivers using chronic treatments influencing driving.

These recommendations were instrumental for the European Commission in launching a Call for Proposals in 2004 [8]. Expected outcomes of the project to be funded are partly related to a classification of medicinal drugs according to their impairing effects on driving, and were stated as follows:

1. Be able to position medicines according to a labelling system corresponding to a European classification which will have been worked out.

2. Define the doctors' legal responsibility vis-à-vis dangerous patients consuming psychoactive substances and the role they can play with regard to road safety.

3. To be in a position to inform the general public, for both preventive purposes and for intervening with the target group.

Within the DRUID Project several Work Packages have been developed to meet its objectives (please see www.DRUID-project.eu). In order to address the

classification of medicinal products Work Package (WP) 4 “Classification” has four objectives:

1. Task 4.1.: To review the existing
    a) classification/categorisation systems and
    b) labelling systems regarding medicinal drugs and driving.

2. Task 4.2.: To propose and agree on the criteria and the methodology on the establishment of a European classification/categorisation system, based on expert consensus.

3. Task 4.3.: To develop a methodology to continuously update the
    a) classification/categorisation system and
    b) labelling system on medicinal drugs and driving.

4. Task 4.4.: To propose a classification/categorisation for the relevant therapeutic groups of medicines available in the market.

Deliverable 4.2.1. will focus on the development of the objectives in Task 4.2.

Use of a classification system

Within the European Union, it is mandatory to carry out studies to assess the effect of a medicinal drug on the fitness to drive and use machinery prior to commercialisation. It is this information, following European Union legislation (Directive 92/27/EEC, updated Directive 2001/83/EEC) [9], which is used to write the Summary of Product Characteristics (SmPC) and the package insert, mentioning the possible effects on fitness to drive or operate machinery. It should be noted that previously, a proposal has been made to classify medicines in three categories (CPMP III/9163/90-EN – adopted 1991), such information being included in section 4.7 of the SmPC, entitled “Effects on ability to drive and use

machines": "On the basis of the pharmacodynamic profile, reported ADR and/or specific studies on a relevant target population addressing the performance related to driving or using machines, specify whether the medicinal product has a) no or negligible influence b) minor or moderate influence or c) major influence on these abilities" [10,11]. Although this categorisation was adopted, no clear instructions were offered as to how it should be carried out. Some guidance was provided earlier on the tests to be used in assessing the impairment of some psychotropic medicines [12]

Review of existing classification systems

DRUID WP 4 Task 4.1 has reviewed the existing classification/categorisation systems and labelling systems regarding medicinal drugs and driving. The results (Deliverable 4.1.1.) were made available to the public after approval by the European Commission. In total, 16 systems were found (Table 1). Some of these categorisation systems are introduced with the support of professional bodies (e.g. Belgium, Germany, Spain II, ICADTS) , whereas other systems only consist of a small list of medicines which are considered to have an effect on fitness to drive (Greece, the Netherlands, Norway, Denmark and Finland). Only one multi-level categorization system also included multi-level warning labels (France II).

Table 1 Comparison of classification and labelling systems (D 4.1.1., 2008)

Origin	# Medicines	Classification	#Categories	Warning label	Legal
Wolschrijn et al. [13]	572	X	7		
Germany	406	X	7		
Belgium	182	X	7		
Spain I (DGT/UVa)	363	X	3		
Spain II (semFYC/UVa)	395	X	4		
France I (CERMT)	508	X	4	X	
France II (AFSSAPS)	311	X	4	X	X
ICADTS	389	X	3		
Portugal	241	X	5		
Greece I (legal)	89	NA	NA		X
Greece II (monographs)	92	NA	NA		
The Netherlands	156	NA	NA	X	
Norway	87	NA	NA	X	
Denmark	83	NA	NA	X	
Finland	68	NA	NA	X	

NA: Not Available – a single list of medicines were identified with no further stratification

In France (AFSSAPS) the number of medicines (France II, Table 1) is labelled at launch, however categorisation has now been assigned for all medicines available on the market. This is similar for Spain (AEMPS), where all medicines available on the market have been categorised in 2 categories, with a legally binding warning lable (see also Table 2).

For France the list of medicines is available at:
http://www.afssaps.fr/Infos-de-securite/Recommandations/Medicaments-et-conduite-automobile-Mise-au-point/(language)/fre-FR

For Spain the list of medicines (with and without pictogram) is available at:
http://www.aemps.es/indFarma/etiqueProspectos/conduccion/listadosPrincipios.htm

Labelling regarding medicinal drugs and driving has been in existence for many years in the Netherlands (a yellow/black label which states “this drug can influence your reactions. Beware when using alcohol” applied by the pharmacist to a list of medicines defined in 1973) and most Nordic countries (a red triangle appearing on a small number of medicines from 1981), except in Sweden where the red triangle was removed from the medicines in 2007.

Dichotomous systems of labelling have no opportunity to differentiate between medicines within one therapeutic class, if differences concerning impairment of driving fitness exist. Therefore, early attempts were made by Wolschrijn, de Gier and de Smet in 1991 to develop a graded-level classification system based upon expert ratings and consensus development [13]. A categorisation of about 570 drug doses/formulations or effects for a certain time-interval after intake (for the hypnotics) was developed using 7 categories.

Belgium was the first country to introduce a multiple level categorisation system for 180 medicines addressing health care professionals and patients [14], followed by Spain [15] and France [17]. These categorisation systems [13-17] were not fully equivalent in either the number of categories or in the substances included.

The labelling of medicinal drugs became widespread in France when the red triangle with a black car inside was first introduced in 1999 (Figure 1). In 2000 a report was published by the Prévention Routière, proposing a four-tier categorisation system for medicines focussing on the driver and his authorisation to drive types of vehicle [16]. New regulation was then introduced in 2005 [17], again with 4 tiers, but introducing three warning categories for patients, which are also reflected by three warning symbols that are printed on the medicine-box (Figures 1 & 2). This categorisation then became legally binding as published in the Official Journal of the French Republic.

The ICADTS categorisation list [18] is based on the Belgium, Spanish and current French categorisation lists, and has proposed three categories.

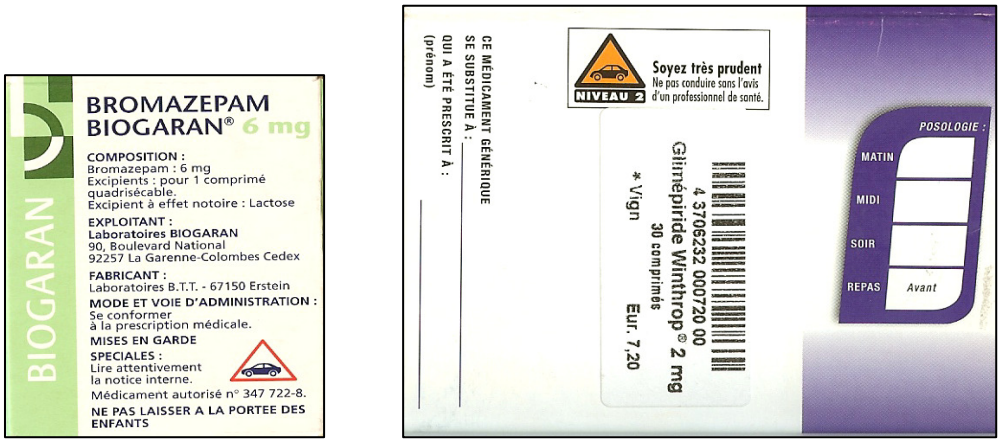

Figure 1. Pictograms on medicinal drugs in France (Left, initial pictogram with a red triangle and a black car. Right, current pictogram for Category 2).

Warning symbol	Description
	Be careful. Do not drive without having read the leaflet. **Soyez prudent** Ne pas conduire sans avoir lu la notice.
	Be very careful. Do not drive without advice of a medical professional. **Soyez très prudent** Ne pas conduire sans l'avis d'un professionnel de santé.
	Attention: danger: Do not drive. **Attention, danger: ne pas conduire** Pour la reprise de la conduite, demandez l'avis d'un médecin.

Figure 2. Categories and warning labels in France (2005)

Establishment of Criteria

Purpose and use

The establishment of criteria for a European categorisation will have to serve most of the needs of all parties involved: health professionals, drug regulatory agencies, drug manufacturers and patients. In general warning symbols are used in different ways in daily life activities (e.g. road traffic, airports, manuals for electronic devices) and most of the time people use these without severe problems. However, general warnings for physicians, pharmacists and patients of a drug's adverse effect on the central nervous system, as provided in package inserts, are more problematic. Normally the lists are extensive and start with "insomnia, dizziness, confusion, nervousness, somnolence, etc." and additional warnings are given. For example it may relate the signs to impairment of mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machines. Furthermore it can alert patients to use caution in such activities until their individual responses to that drug have been well established. Questions how and when these responses are to be determined are unanswered and leave the patient with no clear instruction. At the same time the physicians and pharmacists have no information on how to select the least impairing medicine within a therapeutic class for an individual patient [19].

The dichotomous systems introduced in the Netherlands and the Nordic countries failed to distinguish either between drugs in the same therapeutic class that could have markedly different effects on driving ability or between different doses of the same drugs. These and other deficiencies are probably responsible for the fact that most patients do not alter their driving behaviour in any significant way as a direct result of the labels. A small-scale questionnaire survey of Dutch patients who were receiving psychotropic medications revealed that seventy-five per cent of them did not respond appropriately [20]. Patients reported that they

used less of their medications, interrupted the dosing regimen, or simply ignored the warning because they did not realise it applied to them.

A second study was carried out subsequent to a general public campaign concerning the influence of drugs on driving [21]. A questionnaire was distributed to 1,043 patients who were receiving a drug with a yellow/black label. This study revealed that only thirty per cent of the respondents had changed their behaviour towards driving. The changes included not driving, driving less, and driving more carefully.

The Swedish national pharmacy company Apoteksbolaget AB published an evaluation of the Nordic red triangle system in 1987 [22]. A survey of a sample of the general public was conducted by questionnaire to investigate the understanding of the meaning of the red triangle. The question was asked, “If you see a red triangle on an medicine box, what does that mean to you?” About half of the respondents said they understood it to mean that one should not drive a car when taking such a medicine. The other half thought it was similar to other warnings, such as “keep out of reach of children”, “dangerous” or “poison”.

It is expected that for improving risk communication to patients and health care professionals more information will be needed than just a warning symbol. Initiatives towards a new system will be built on the experiences that have been collected so far but are not well documented. The first step in addressing the needs for a new system is to know more about criteria that will assist the establishment of a European system based on consensus.

Criteria based on use and target population

The development of the categorisation systems as described on page 15 shows that different purposes were served by developing the different categories and warning labels. The categories developed by Wolschrijn et al. [13] served the purpose of developing consensus for the first time among the scientists involved in experimental human psychopharmacological research. It was clear that

consensus was derived for many frequently used drugs and dosages with descriptions that would satisfy the needs of the scientists to agree on the descriptions of seven categories. Emphasis was on impairment descriptions agreed upon by the scientists based on results in experimental studies, and not on the information presented to patients or health care professionals.

Another more recent experience that shows how warnings are perceived and why target populations are crucial in developing a system is the French classification. In 1999 a warning label (red triangle with black car) was introduced to indicate the potential effects on driving performance for all drugs with impairing properties. This system did not last long, because it was believed that the system had several significant downsides:

1. There was no subdivision between less and more severely impairing medication.

2. Patients and doctors did not receive an explanation about the practical implications of the warning label.

3. The symbol appeared on over 4,000 medicines (one out of three available on the market) and therefore largely lost its meaning.

Because of these downsides, a new classification with 3 warning categories and symbols (Figure 2) was introduced in 2005. It shows indications on the 3 categories underneath the symbol for the colour-blind patients and clear instructions what to do in writing next to the symbol. It was published in the 'Journal Officiel de la République Française' and therefore legally binding. 1120 medicines were assigned to category 1, 1573 to category 2 and 187 to category 3. On average 63% of pharmaceutical specialities on the French market were without any pictogram (AFSSAPS, Mise au point, Médicaments et conduite automobile, AFSSAPS, mars 2009).

Establishment of criteria

In discussing the establishment of criteria for a European categorisation, based on expert consensus, it is important to realize that differences exist in the purpose and meaning of the various classification systems, whereas they basically are derived from the scientific consensus report by Wolschrijn et al. The first step in establishing the European system would be to discuss the criteria from the different perspectives and to conclude on the steps to follow. An overview of these perspectives is presented in Table 2.

Table 2. Overview of perspectives in some classification systems

Origin	Number of Categories	Warning symbol	Description	Practical use	Legally binding
Wolschrijn, e.a. (1991) [13]	7	-	Impairment described from no, minor, moderate, not severe, severe to unknown, based on outcomes of experimental studies rated by experts in experimental human psychopharmacology. Drug doses and formulations were taken into account.	Selection of the least impairing medicine within one therapeutic class is possible, however information was not presented to health care professionals	-
Belgium (1999) [14]	7	-	Same as in Wolschrijn et al.	Selection of the least impairing medicine within one therapeutic class is possible. For each substance a monograph was written based on a literature search. Brochures were provided to health care professionals and the public.	-
ICADTS (2001) [24]	3	-	Impairment description for medicines: cat. I Presumed to be safe or unlikely to produce an effect; cat. II Likely to produce minor or moderate adverse effects; cat. III Likely to produce severe or presumed to be potentially dangerous	In order to make physicians, pharmacists and patients aware of the meaning of each category a comparison to the impairing effect of alcohol is suggested: cat I BAC < 0.2 g/l; cat. II BAC 0.2-0.5 g/l; cat. III > 0.5 g/l	-
France (2000) [16]	4	X (General, red triangle with black car)	Category 0 (Currently no effects on driving performance are known). Other descriptions refer to the authorisation to drive with light and heavy driver's licences (Cat I), light but not with heavy (Cat II), and incompatible with any driver's licence (Cat III).	Focussed on the driver and his authorisation to drive according to driver's licence. With specific directions to contact the medical commission for granting an exception.	X (General symbol)

Spain (2001/2002) [15]	3	-	Three categories were considered (see ICADTS 2001). The categorisation was based on the information in the package insert (package leaflet) and the Summary of Product Characteristics of medicines commercially available in Spain.	Information was aimed at supporting physicians in selecting the least impairing medication.	-
Spain (2004) [27]	4	-	Based on previous development in 2001, a fourth category was introduced (0: Medication not affecting driving performance).	It was considered that health care professionals needed a fourth category. Brochures were provided to the health care professionals.	-
France (2005) [17]	4	X (For top three categories, a black triangle with car and coloured background)	Clear description for patients what to do and when to ask advice from a medical professional. For colour-blind patients the categories are mentioned underneath the symbol.	Selection of the least impairing medicine within one therapeutic class is possible. Since symbols are printed on the medicine box all health care professionals are aware.	X (Three categories)
ICADTS (2007) [18]	3	-	Summary of the three categories described by Wolschrijn (as used in Spain) with interpretation as given by original report (1991), and combination with French advices for patients for each category.	Selection of the least impairing medicine within one therapeutic class is possible. For most frequently used drugs the interpretation for each category has been supported by comparing the medicinal drug effects with the effects of a equivalent blood alcohol concentration.	-
Slovenia (2008) [25]	3	X Medicines with major	Three categories have been assigned to impairing medicines: cat. a) no or negligible influence; cat. b) minor or moderate influence;	Selection of the least impairing medicine within one therapeutic class is possible. Since symbols are printed on the medicine box all	X (two categories)

		influence are labelled with a filled red triangle; medicines with minor to moderate influence are labelled with an empty triangle	cat c) major influence on driving fitness (based on SmPC guideline descriptions prior to September 2009.)	health care professionals are aware.	
Spain (2007) [23]	2	X (red triangle with car inside together with text "*driving: see package insert"*	Two categories, those which do have an effect and those which do not.	Provision of specific information for individual medicines to inform healthcare professionals and patients	X

Note: For references to more information about the origin of classification systems, please see the report of WP4 Task 4.1. (Deliverable 4.1.1.)

New legislation concerning driver-impairing medicines has recently been approved in Spain [23]. It includes the introduction of a warning label on medicines that can impair driving. The label consists of a black car inside a red triangle together with the following text: *driving: see package insert*, so it is very similar to the first French warning label although is not targeted at specific drivers. To review the criteria, procedures and list of substances the website of the Spanish Medicines Regulatory Agency's website can be visited:(http://www.aemps.es/indFarma/etiqueProspectos/conduccion/home.htm).

The overview (Table 2) clearly shows the evolution in the development of the classification systems with the following milestones at the extremes:

1. an effort to achieve consensus about the categories and descriptions from a scientific perspective without addressing the target groups more specifically, that served as the starting point for many other classification, to

2. an effort to introduce warning symbols and directions for patients, as end-users, in a legal framework.

If considering this evolution as starting point for our discussions on establishing criteria, some observations need attention:

1. The first efforts were based on consensus development and evidence based literature search with the following limitations:
    a) the "presumed" categories (I*, II*) in the Wolschrijn approach were included to allow classification of medicines where sufficient experimental studies are lacking to support this presumption and to establish more defined categorisation and where categorisation was also based on pharmacological profiles of the substances involved;
    b) the Belgian experience showed that 42% of the substances were in the "presumed" categories, where lack of data and the diversity of study designs were causing some problems in completing the work.

2. Looking at the French development it was clear that the first and foremost intention of the categorisation was to support the patient where:
    a) it was concluded from a first experience that a general warning symbol did not satisfy the needs because no distinctions could be made between medicines with less or severely impairing properties;
    b) patients and doctors were not provided with clear information about the practical implications of the general symbol.

This resulted in the development and implementation of a four tier category system with levels 0, 1, 2 and 3, where clear directions for patients were printed next to the warning symbol for categories 1 to 3 on the product label.

3. The frameworks used for categorising the individual medicinal drugs in the various systems are not very transparent with respect to how the decisions on individual medicines are derived, where:
    a) the French system with four categories has a framework for assigning medicinal drugs to respective categories. Valuable experiences for further discussion are to be expected from researching this system;
    b) evidence based medicine is a most preferred way of looking at the categorisation of medicinal drugs, but much has to be decided on the different ways that exist in the development and implementation of evidence-based tools for informing patients and healthcare professionals. Task 4.2 is a challenge to make that clear because evidence is not always available, but at the same time health care practice can benefit from existing knowledge and expertise available for some drug classes (e.g. benzodiazepines, antidepressants, antihistamines);
    c) it is unclear how present systems of collecting information on side-effects of medicinal drugs (pharmacovigilance networks) can be used to support the classification of existing individual medicines, whilst accepting the lack of sufficient information in the introduction of new chemical entities at the time of product licensing prior to placing on the market.

In conclusion, it is clear from the developments and experiences in various countries that classification of medicinal drugs by their potential to influence driving ability is possible, needed and well accepted by all parties that have an interest in the safe use of medicines.

Outcomes of Expert Meetings

One of the objectives of Work package 4 (Classification) within the DRUID-project was to propose and agree on the criteria and methodology for the establishment of a European classification/categorisation system and labelling system for medicinal drugs that can affect driving performance. Based on the discussion of outcomes of Task 4.1 (Review of existing classification efforts, see also Deliverable 4.1.1.), the establishment of criteria for a European categorisation based on expert consensus was undertaken in Task 4.2. It was decided to address the Pharmacovigilance Working Party (PhVWP) based at the European Medicines Agency (EMA) with a request to participate in the discussions, since patient safety affected by medicines' adverse reactions within a European context would be the primary focus. By organising two small-scale invitational workshops (Paris, February 2008, and The Hague, June 2008) and one consensus meeting (Lisbon, November 2008), outcomes of these meetings could be presented for further discussion with the PhVWP and representatives within DG TREN and DG SANCO.

Proposal for harmonised criteria

Since the European directive of October 26th, 1983[1] was issued, the effects of medicinal products on the fitness to drive and to use machines have been identified in a special section of the Summary of Product Characteristics (SmPC). In the note of October 16th, 1991[2], the Committee for Medicinal Products for Human Use (CHMP) of the European Agency specified that, for medicinal products authorised after January 1st, 1992, section 4.7 should be defined on the basis of their pharmacodynamic profile, undesirable effects and/or effects on the fitness to drive.

[1] 83/570/CEE
[2] III/9163/90-EN

For the development of Task 4.2 it was concluded that this general approach should be more specific and that a proposal for harmonised criteria in order to agree on a categorisation was needed. The proposal for achieving this is based on discussions during the meetings with the experts and in WP4 meetings and yielded the following conclusions:

1. It was underlined that the SmPC is intended for the healthcare professional, although its wording would have to be interpreted for the patient by the doctor during consultations, and is required to be translated into layman's terms in the patient leaflet. But the section on impairment of the fitness to drive (section 4.7) needed an update to make it clear and more detailed, explaining four possible descriptions of levels of influence and circumstances that needed more attention. The following proposal was sent to the EMA for consideration by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)), as a response during the consultation phase of the revision of the SmPC guidelines in February/March 2008 (changes are indicated in red):

> *4.7 Effects on ability to drive and use machines*
>
> *On the basis of the pharmacodynamic and pharmacokinetic profile, reported adverse reactions and/or specific studies in a relevant target population addressing the performance related to driving and road safety or using machines, specify whether the medicinal product has a) no or negligible influence b) minor; c) moderate influence or d) major influence on these abilities. Effects of the disease itself on these abilities should only be discussed in exceptional circumstances. Other important factors that affect the ability to drive and use machines should be considered if relevant, e.g. duration of the impairing effect and the development of the tolerance of adverse reactions with continued use. For situations b, c and d, special warnings/precautions for use should be mentioned.*

However, the SmPC guidelines finally adopted in September 2009 (which applies as from 1st of May 2010) showed one difference if compared with the proposal by

the DRUID experts; the last lines read now as follows: "*For situations c and d, special warnings/precautions for use should be mentioned here (and also in section 4.4 for situation d).*" Special warnings/precautions for situation b) are not foreseen. However, sensitivity to minor side effects that impair driving can differ from patient to patient. Therefore patients should be warned not to drive if important impairment occurs or persists.

For further details, please visit:
http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm
http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

It is emphasised that the information which is reported in the SmPC, the patient leaflet and on the product package has to be consistent. The information that is made available for the patient in the leaflet is based on information contained within section 4.7 of the SmPC.

2. Based on the experiences in countries where a categorisation has been implemented, either as official directive for labelling, such as in France, or for supporting the development of information materials for health care providers and patients, such as Spain and the Netherlands, WP4 partners agreed that the categorisation system derived from the SmPC is in line with the developments in those countries. Therefore the WP4 partners agreed on the acceptance of these four categories (a – d in the SmPC, 4.7).

It is proposed that next to the categorisation scheme with four categories, (levels 0, 1, 2 and 3) warnings should be applied to the top 3 categories creating a three level warning/information system, whereas a warning for the lowest tier would not be considered necessary. This would be applied for the purpose of informing health care professionals and patients.

In the current situation where similar categorisations exist, for example in France, Spain and The Netherlands, there are different approaches:

- In France the three level warning symbols on the package are aimed at guiding patients to take the right decision after obtaining the information from the leaflet or by asking their physician or pharmacist.

- In the Spain, three levels continue to be used to inform physicians, pharmacists and patients about possible risks and safer alternatives, if available. The three levels are also used to advise the prescribing physicians and dispensing pharmacists to give the appropriate advice to the patient using a drug with impairing properties.

- Currently in the Netherlands, three levels are used for deciding on requirements for issuing driving licences, since an update of rules (established in 2000) in 2008 [28] and for informing dispensing pharmacists and prescribing physicians about possible risks and safer alternatives, if available. The three levels are also used to advise the prescribing physicians and dispensing pharmacists to give the appropriate advice to the patient using a drug with impairing properties [29].

Classification of active substances

During the expert meetings it was suggested to build on the experience from the French AFSSAPS experts in categorising medicinal drugs affecting driving performance.

In this approach it is stated that the risk of impairment after taking a medicinal product on the fitness to drive depends on several factors:

1. the pharmacodynamics and pharmacokinetic profile of the medicinal product combined with the adverse effects, knowing that the more profound or

prolonged these effects are, the more influence it will have on the patient's fitness to drive safely;

2. individual sensitivity, the same dose of the same active substance can have variable effects according to subjects' sensitivity to the substance (example: systemic antihistamines and sedation);

3. conditions of use: active substance presentations and strength, indications, posology, route of administration (oral, parenteral, immediate-, or sustained release), as well as short or long-term usage, interactions with other medicinal products, interaction with alcohol, etc..

As a consequence, each of these factors cannot be considered separately and the level of risk attributed to a medicinal product shall be the result of all these factors. The categorisation will have to reflect the overall impairment of these factors on the fitness to drive.

In summary, categorisation of active substances by experts includes several steps of evaluation:
1. Pharmacodynamic and pharmacokinetic data
2. Pharmacovigilance data
3. Experimental and epidemiological data
4. Additional data
5. Synthesis

Description of categories

It was pointed out by experts during the workshops that the information that is reported in the SmPC, the patient leaflet and on the product package has to be consistent. Section 4.7 of the SmPC must be clear, as the information that is available for the patient will be derived from this section. There are, however, still

vague descriptions in leaflets, especially when it is stated in the SmPC (section 4.7) that there are no studies available on the possible impairing effects of the product. Therefore the participants during the invitational workshops emphasised that the SmPC should mention the categorisation. It is obvious that the assessors within the regulatory bodies, while reviewing the documents in the Application Dossier of the product, need to be able to define what a minor, moderate or severe effect is. Therefore it is suggested that the following decision making procedures for assigning categories will be considered by regulatory agencies and responsible manufacturers (Table 3).

Table 3. Assigning categories based on decision making

SmPC Descriptions*	**Assessing the category based on the following:**	**Supported by outcomes of the 5-steps:**	**Supported by comparison with alcohol (source: ICADTS website)**:**
a) No or negligible influence	**Conclusion from reviewing the scientific literature:** In various experimental studies negligible or no impairment of driving performance or performance related to driving is repeatedly demonstrated. In epidemiological studies negligible or no significant increased risk of involvement in traffic accidents is repeatedly demonstrated. **Presumed not to be dangerous** based on the drug's pharmacological profile, even though there are no experimental studies that support this	1. Pharmacodynamic and pharmacokinetic data: no influence expected. 2. Pharmacovigilance data: no demonstration of CNS side effects or other unwanted effects that impair driving. 3. Experimental and epidemiological data: no demonstration of impairment. 4. Additional data: no further data on impairment. 5. Synthesis: no or	No sufficient data available that will allow comparison with the effects of alcohol.

	presumption.	negligible influence.	
b) Minor influence	**Conclusion from reviewing the scientific literature:** Some impairment of driving performance or performance related to driving is seen in some experimental circumstances. In epidemiological studies a slight but non-significant increased risk of involvement in traffic accidents is (not frequently) demonstrated. **Presumed to produce no or at the most minor adverse effects** but because of a lack of sufficient experimental studies it cannot be established if the effect is minor or absent.	1. Pharmacodynamic and pharmacokinetic data: minor influence expected. 2. Pharmacovigilance data: some demonstration of CNS side effects or other unwanted effects that impair driving. 3. Experimental and epidemiological data: some demonstration (not consistent) of impairment. 4. Additional data: some data on possible impairment. 5. Synthesis: minor influence	Likely to produce minor adverse effects on driving ability. This impairment is comparable to a blood-alcohol concentration of > 0.0 - < 0.5 g/l.
c) Moderate influence	**Conclusion from reviewing the scientific literature:** An impairment of driving performance or performance related to driving is seen in various experimental circumstances. In epidemiological studies a significant increased risk of involvement in traffic accidents is demonstrated. **Presumed to produce**	1. Pharmacodynamic and pharmacokinetic data: moderate influence expected. 2. Pharmacovigilance data: demonstration of CNS side effects (not severe) or other unwanted effects that impair driving. 3. Experimental and epidemiological data:	Likely to produce moderate adverse effect on driving ability. This impairment is comparable to a blood-alcohol concentration of 0.5 - 0.8 g/l.

	moderate adverse effects but because of a lack of sufficient experimental studies it can not be established if the effect is minor or moderate.	demonstration of impairment (not severe). 4. Additional data: various data on impairment. 5. Synthesis: moderate influence.	
d) Major influence	**Conclusion from reviewing the scientific literature:** In various experimental circumstances gross impairment of driving performance or performance related to driving, is repeatedly seen. In epidemiological studies a significant and very meaningful increased risk of involvement in traffic accidents is demonstrated. **Presumed to be potentially dangerous** based on their pharmacological profile, even though there are not sufficient experimental studies to support this presumption.	1. Pharmacodynamic and pharmacokinetic data: severe influence expected. 2. Pharmacovigilance data: demonstration of CNS side effects (severe) or other unwanted (severe) effects that impair driving. 3. Experimental and epidemiological data: demonstration of impairment (severe). 4. Additional data: data on impairment (severe). 5. Synthesis: major influence.	Likely to produce severe effects on driving ability or presumed to be potentially dangerous. This impairment is comparable to a blood-alcohol concentration of >0.8 g/l.

*Descriptions apply to the use of the medicine in normal treatment conditions (excluding misuse) at the start of treatment.

**www.icadts.org

Experimental studies for assessing a medicinal drug's effect on driving or skills related to driving

Methodological guidelines concerning adequate design of studies on drugs and driver fitness are described by an ICADTS Working Group in 1999. These guidelines are not intended to restrict research on a few established methods but provide investigators with a minimum set of quality-assured, acceptable guidelines.

The ICADTS document is specifically addressed to pharmaceutical manufacturers and medicinal drug regulatory authorities that share the responsibility for ensuring the safe use of medicines by patients who operate motor vehicles. The guidelines presented by experts in the field will lead to a standardised assessment of each (new) medicinal drug's hazard potential for driving as part of the documentation submitted for the registration process. In this ICADTS document it is stated that programmatic research should support the categorisation of the medicine's hazard potential using a simple scheme that will be understood by the prescribing physician, dispensing pharmacists, and ultimate users.

The ICADTS document can be downloaded from the ICADTS website:
http://www.agnp.de/AGNP-Homepage-Dateien/Arbeitsgruppen/AG_Verkehr_icadts.htm

Possible side effects related to driving

During the activities in Task 4.3 on categorisation of the existing medicines, the occurrence of unwanted effects was considered as key information for categorising some medicines, in circumstances that information on experimental studies for assessing a medicine's effect on driving or skills related to driving or epidemiological data were lacking. For that reason, section 4.8 of the SmPC, entitled "undesirable effects" which lists reported adverse effects or reactions,

was used (as well as specific literature searches), if necessary. The EMA adheres to a Quality Review of Documents (QRD) convention (regularly updated in line with the SmPC) which lists frequencies of adverse reactions as follows

- very common (≥1/10)
- common (≥1/100 to <1/10)
- uncommon (≥1/1,000 to <1/100)
- rare (≥1/10,000 to <1/1,000)
- very rare (<1/10,000)
- not known (cannot be estimated from the available data)

DRUID Partners have taken into account this convention of defining frequency of undesirable effects in their categorisation framework for medicines and driving. Firstly by considering those effects categorised as very common (≥1/10) and common (≥1/100 to <1/10), and secondly, those undesirable effects that can potentially impair the fitness to drive safely.
In case rare or very rare unwanted effects or certain severely impairing effects occur, for example sudden sleep attacks, DRUID Partners recommend that this should be mentioned in the patient information leaflet.

The following criteria were used for assigning a medicine to a specific category, in case experimental or epidemiological data are lacking (Table 4).

Table 4. Relationship of the undesirable effects category in the SmPC to the DRUID categorisation system

Declaration of undesirable effects that can potentially impair the fitness to drive safely	**DRUID Category**
Very common (≥ 1/10)	Category 2 or 3
Common (≥1/100 to <1/10)	Category 1
Rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000)	Category 0

In Table 5 all relevant potentially undesirable effects to be considered when categorising the effects of medicines on driving are listed.

Table 5. Undesirable effects that can impair the fitness to drive grouped by system organ class

System organ class	**Selection of undesirable effects that can impair the fitness to drive safely**
Nervous system disorders	▪ Somnolence, dizziness, drowsiness ▪ Confusion - cognitive disorder- disorientation – co-ordination disturbances ▪ Involuntary movement disorders: ataxia, tremor, Parkinsonism, acute dystonic (dyskinesia) and dyskinetic reactions (dystonia) ▪ Convulsions – seizures ▪ Muscle weakness
Psychiatric disorders	▪ Perception disturbances (hallucination, visual hallucination, auditory hallucination, illusion) ▪ Psychotic reactions and psychotic disorder (including paranoia psychosis) ▪ [Other: Emotional lability, mood swings, aggression, nervousness, irritability, personality disorders, thinking abnormal, abnormal behaviour, euphoric mood, restlessness (emotional state of excitement), depersonalisation]
Eye disorders	▪ Diplopia or double vision ▪ Blurred vision ▪ Accommodation disorders ▪ Visual acuity reduced ▪ Photophobia ▪ [Other: visual field defect, peripheral vision loss, altered visual depth perception, oculogyric crisis].
Ear and Labyrinth disorders	▪ Vertigo ▪ Hearing loss ▪ [Other: buzzing, tinnitus]
Metabolism and nutrition disorders	▪ Hypoglycaemia
Vascular disorders	▪ Hypotension

Important note: If some side effects occur at the start of treatment or if tolerance over time to the occurrence of such undesirable effects can be expected, this should be mentioned in the Patient Information Leaflet.

Input for discussing a European categorisation system

Consensus on Categories and Warning levels

The experts involved in discussing input for a European categorisation system and WP4 partners agreed on 4 categories to inform the patient and the health care providers on the drug's impairing effects on driving. These are derived from the revised version of the SmPC, as proposed to CMD(h) in March 2008 during the consultation phase for the guideline on the SmPC.

Based on these 4 categories, information for physicians and pharmacists can be derived, where the comparison with the impairing effects of various levels of alcohol is suggested for communicating severity of impairment. It was, however, emphasised by the experts and WP4 Partners that a comparison with a recreational drug such as alcohol may not be appropriate, as a medicine is a necessity for a patient.
Based on the 4 categories, warning levels to inform patients can be developed. It was emphasised any warning based on warning symbols or pictograms, should always have a description or explanation in writing as an integral part of the overall warning symbol.

The following scheme (Table 6) is presented as input for discussing a European categorisation system, based on the conclusions by the experts from Drug Regulatory Agencies and WP4 Partners. This table takes into consideration the information that assessors need to review during categorisation of individual medicines and provides proposals for the wording in the Patient Information Leaflet.

Table 6. Input for discussing a European categorisation system

Categorisation based on SmPC section 4.7	**Data to be used for assigning the category**					**Wording for SmPC and Package Information Leaflet**	**Information for physicians and pharmacists**		**Warning for patients (based on warning symbols)**
	Pharmaco-dynamic & -kinetic data	**Pharmaco-vigilance data**	**Experimental & epidemiology data**	**Additional data**	**Synthesis**		**Description of categories ***	**Information on how to advise their patients**	
Unknown	No sufficient data available that will allow categorisation	No sufficient data available that will allow categorisation	No sufficient data available that will allow categorisation	No sufficient data available that will allow categorisation	No categorisation possible	{Invented name} has unknown effects on the fitness to drive and use machines. Data on reported side effects that impair driving are insufficient.	**Unknown**	Inform that the medicine's adverse effects on driving are not known due to a lack of sufficient data	Warnings are not possible because of a lack of information on impairment of fitness to drive
a) No or negligible influence	No influence expected	No demon-stration of CNS side effects or other	No demon-stration of impairment	No further data on impairment	No or negligible influence	{Invented name} has no or negligible influence on fitness to drive	**Category 0** Presumed to be safe or unlikely to produce an effect	Confirm that the medicine will be safe for driving, provided that combinations with alcohol and	[no warning needed]

		unwanted effects on driving				and use machines	on fitness to drive.	other psychotropic medicines are excluded.	
b) Minor influence	No influence expected	Some demonstration of CNS side effects or unwanted effects that impair driving	Some impairment in some experimental studies. Slight increased risk demonstrated in epidemiological studies	Some data on possible impairment	Minor influence	{Invented name} has minor influence on fitness to drive and use machines. Do not drive if side-effects that impair the fitness to drive occur or persist (e.g. dizziness, fatigue, decreased attention).	**Category 1** Likely to produce minor adverse effects on fitness to drive	Inform the patient that impairing side-effects may occur especially during the first days that have a negative influence on their fitness to drive. Give the patient the advice not to drive if these side-effects occur.	**Warning level 1** Do not drive without having read the relevant section on driving impairment in the leaflet. Avoid combination with alcohol and /or illicit drugs (will potentiate risk). Check combinations with other medicines that could enhance impairment (ask your pharmacist or physician)
c) Moderate influence	Moderate influence	Demonstration of CNS side	Impairment of driving	Various data on	Moderate	**{**Invented name} has moderate	**Category 2**	Inform the patient about the possible	**Warning level 2**

	expected	effects (not severe) or unwanted effects that impair driving	performance is seen in various experimental studies. In epidemiological studies a significant increased risk is demonstrated	impairment (not severe)	influence	influence on fitness to drive and use machines. Do not drive without advice of a health care professional. It is advised not to drive the first few days of the treatment.	Likely to produce moderate adverse effect on fitness to drive.	impairing side-effects and the negative influence on their fitness to drive. Advise the patient not to drive during the first few days of the treatment. If possible prescribe a safer medicine, if medical considerations allow and acceptable by the patient.	Do not drive without advice of a health care professional. Read the relevant section on driving impairment in the leaflet before consulting the physician or pharmacist. Avoid combination with alcohol and /or illicit drugs (will potentiate risk). Check combinations with other medicines that could enhance impairment (ask your pharmacist or physician)

d) Major influence	Severe influence expected	Demonstration of CNS side effects (severe) or unwanted effects that impair driving	Gross impairment of driving performance or performance related to driving is repeatedly seen. In epidemiological studies a significant and meaningful increased risk is demonstrated	Data on severe impairment	Major influence	{Invented name} has major influence on fitness to drive and use machines. Do not drive. Seek medical advice after a period of treatment about the conditions to restart driving again.	**Category 3** Likely to produce severe effects on fitness to drive or presumed to be potentially dangerous.	Inform the patient about the possible impairing side-effects and the negative influence on their fitness to drive. Urgently advise the patient not to drive. Consider prescribing a safer medicine, if medical considerations allow and acceptable by the patient.	**Warning level 3** Do not drive. Seek medical advice after a period of treatment about the conditions to restart driving again. Avoid combination with alcohol and/or illicit drugs (will potentiate risk). Check combinations with other medicines that could enhance impairment (ask your pharmacist or physician)

***Categories apply to the acute or first time use of the medicine in normal treatment conditions (excluding misuse) at the start of treatment.**

More attention given by health care providers

DRUID prescribing and dispensing guidelines have been developed within Work Package 7. During the invitational workshops emphasis was given to motivate health professionals to provide patients with clear information allowing them to make their own judgements and to decide whether it is safe for them to drive. This is especially important for those who are advised to use a category 2 or 3 medicine. It was suggested that prescribing physicians should always address the individual circumstances and needs of the patient. Pharmacists are in general able to explain the drug effects in relation to the drug's pharmacodynamics and pharmacokinetics (also in case of drug-drug interactions) and will be able to assist patients in taking their medication appropriately (also focusing on adherence to treatment regimen).
Any advice to the patient would ideally be the result of an evaluation of these needs and the medical condition that will be affected by medicines in a positive way, whereas at the same time negative adverse effects (e.g. sedation, vertigo, blurred vision) on driving fitness might occur. However, the medical condition of the patient may present its own risks on fitness to drive, which should also be taken into account.

In many occasions, a psychoactive effect of a required medicine can be unavoidable and physicians will ask patients for caution at the start of treatment, patient self-evaluation before driving and evaluation of the potential risk. Any advice given to the patient will be based on recognition of established effects on the patient's fitness to drive. In some cases, neither the medicine nor the disease will be the cause of concern, rather the management of therapy (e.g. insulin in diabetes mellitus). In those situations, advice is aimed at training and education of the patient.

It is obvious that when patients are advised to read the relevant sections in the package leaflet (with or without a warning on the package to do so), health care providers need to be prepared to answer questions about the text written in the

leaflets. At this moment the section in the leaflet of psychotropic medicines is not always clear about the impairing effects and how to react to these with respect to driving. In many cases the package information leaflet (PIL) instructs a patient-driver to observe the impairing side-effects, which is difficult for most patients. Therefore it is emphasised by the experts and WP 4 Partners to make a distinction in proposing the European categorisation system:

1. In considering the ***present*** situation, any advice provided to the patient on the label to read the package leaflet before driving will result in raising more questions than obtaining answers on how to react. This is because the information obtained from the leaflet concerning effect on driving ability is highly variable in quality and clarity. Therefore physicians and pharmacists are advised to explain the problem before patients are confronted with them.

2. In considering the ***future*** situation, where leaflets are derived from a SmPC with clear explanations on the category, advice to read a package leaflet will result in more consistent dissemination of information and a better opportunity for patients to make the right decision on their fitness to drive or operate machinery.

Finally, it is emphasised that consultations between patients and their healthcare provider need special attention with regards to providing clear advice on fitness to drive. Emphasis also needs to be made to share decision-making between patient and physician and document that decision.

Moving forward in Europe

Progress and steps forward

After the development of the input for establishing criteria for a European categorisation system in this Deliverable, progress and steps forward have been achieved in discussing these proposals with the PhVWP, whose meetings are held monthly at the EMA. During two visits of the Task 4.2 leader and WP4 leader to the PhVWP in London in June 2010 and follow-up discussions with two more WP 4 Partners in December 2010, the PhVWP developed a consensus view through sub-group meetings on 15th of February 2011 and in March 2011.

The PhVWP came to a consensus that a common approach should be developed which:

- Takes into account scientific evidence.
- Recognises different national approaches and experiences.
- Acknowledges the difficulty of having a consistent classification for all medicines based on current scientific evidence.
- Ensures that any information on the influence of medicines on fitness to drive should be simple and patient-centred, and therefore should be reflected in the Patient Leaflet, although information directly provided to the patient by prescribers and/or pharmacists is very relevant.
- Recognises that in addition to the legal, social, medical, and pharmacological aspects of the issue, individual responsibility of the patients plays an important role that should be considered and reflected in the appropriate way in the product information of any medicine.

Currently national approaches differ substantially: from France at one end of the spectrum where labelling with pictograms on the medicine box at three levels

according to impairing properties of the medicine was enforced in 2005, to Sweden at the other end where labelling with the red triangle was removed from medicines in 2007. Sweden amended their labelling in response to patient surveys which revealed that the red triangle pictogram was misunderstood, and therefore replaced the pictogram with a generic warning in the patient leaflet.

In France, a study on prescription medicines and the risk of road traffic accidents showed that warning messages appear to be relevant in particular for medicines with a moderate and major risk (level 2 and 3) of road traffic accidents [26]. This study provides strong evidence of the need for health care providers to give patients good information on the potential effect of any medicine that they are prescribed or taken on their driving fitness. However, this study also showed that the risk of accident for patients who had taken a medicine described as having minor influence on fitness to drive, was no different to those patients that had taken medicines with no or negligible influence. Therefore the necessity for additional warnings for these medicines was not evidence based. Similarly the difference in risk between patients taking medicines with moderate influence did not differ from patients who had taken medicines described as having a major influence. The warnings also currently used in France for these two categories were also considered to be very similar. Consequentially, the PhVWP concluded that a single warning was required for those patients who had taken medicines described as having major or moderate influence on fitness to drive.
A similar study was also undertaken within the Netherlands with similar findings (DRUID Deliverable 2.3.1) where the risk of accident was only considered significant for categories of level 2 and above.

Information on impairment of fitness to drive in the Patient Leaflet

A consensus within the PhVWP that the evidence supported a 2 tier framework would be developed as a basis for warnings to be presented to the patient through the Patient Leaflet. This differentiates between medicines with a potential influence on driving and those which do not. This framework was proposed as follows:

> **Level 1**: General advice on personal responsibility to decide on fitness to drive and the need to read all the information in the leaflet (supported by information available in section 4.7 of the SmPC and reflected in the Patient Leaflet). Proposed standard wordings for the Patient Leaflet for medicines without a potential relevant influence on driving, i.e. based on current SmPC guideline descriptions of level of influence as: a) no or negligible influence or b) minor influence[3]:
>
> *"Read all the information in this leaflet for guidance, (especially section 4). Since the response to a medicine may be individual and your fitness to drive can be affected by other factors, talk to your doctor or pharmacist if you need more information.*
>
> *You need to be sure that you are in a fit condition to drive a motor vehicle or perform other tasks that require high levels of concentration."*
>
> Note: Certain types of products can be exempted from any labelling due to their nature (e.g. vitamins, physiological saline, etc).

This general warning was considered necessary to ensure that patients take responsibility for managing their therapy and assessing their driving fitness. Further information concerning the side effects of medicines is available in section 4 of the leaflet.

[3] A consultation with stakeholders would still be necessary before a standard wording reaches a formal agreement.

Level 2: A warning for medicines with the potential for moderate or major influence on fitness to drive (supported by information available in section 4.7 of the SmPC and reflected in the Patient Leaflet). Proposed standard wordings for the Patient Leaflet for medicines with a potential relevant influence on driving, i.e. based on current SmPC guideline descriptions of the level of influence as: c) moderate influence or d) major influence:

"{Invented name} may affect your fitness to drive or use machines safely.

Read all the information in this leaflet for guidance, (especially sections 2 and 4). Since the response to a medicine may be individual and your fitness to drive can be affected by other factors, check with your doctor or pharmacist for more information.*

You need to be sure that you are in a fit condition to drive a motor vehicle or perform other tasks that require high levels of concentration."

Notes:

- A sentence in line with the information in section 4.7 of the SmPC of each medicine should be added.
- For products with a special warning in section 4.4[4] of the SmPC, i.e. category d) major influence according to the EU Guideline on SmPCs, this information should be reflected in the Patient Leaflet.

*Section 2 of the leaflet contains all warnings and precautions that patients should be aware of before taking their medicines.

More action-oriented warnings and advice to aid awareness were supported. The inclusion of the direction to "Check with your doctor or pharmacist" would act as a reminder to the patient after visiting their doctor and pharmacist. It was anticipated that the doctor and pharmacist will have alerted the patient through general product information guidance, and/or prescribing and dispensing systems

[4] Section 4.4 contains: Special warnings and precautions for use

to inform the patient about a possible time after using the medicine, where it is advised not to drive (e.g. not to drive x hours after intake of a hypnotic). For some products, a stronger advice for an “ad hoc” consultation with a healthcare professional may be warranted in case the advice was not given at the time of the prescription/dispensation, and the inclusion of the direction to “Check with your doctor or pharmacist before driving while using this medicine” would be appropriate. In France category d) medicine shows a pictogram on the medicine box with a side text “Attention: danger. Do not drive. Seek medical advice before driving again”. However, legal differences exist between countries in the use of medicines and driving which can have an impact on both the patient and the healthcare professional, therefore the instruction “Do not drive” was not considered to be appropriate for use across Europe, as patients might fear legal consequences.

Information needs for assigning risk categorisation levels

It was agreed that the preliminary recommendations from DRUID on the criteria for categorisation are of relevance. All sources of evidence should be used, including:

- Data on the pharmacodynamics / pharmacokinetics
- Pharmacovigilance data
- Experimental and epidemiological data
- Additional information

Combining all these sources of evidence into one overview to support the assessment of medicines into the PhVWP proposal, the following key components can be presented (Table 7).

Table 7. Combining risk categorisation levels with information required for assigning levels in the Patient Leaflet

Risk categorisation level in Patient Leaflet	Pharmaco-dynamic & -kinetic data	Pharmaco-vigilance data	Experimental data	Epidemiology data	Additional data
LEVEL 1 **a) No or negligible influence** **b) Minor influence**	No influence expected	No demonstration to low frequency of key side effects that impair driving	No or some non-significant demonstration of impairment in experimental studies.	No demonstration of increased risk to non-significant increased risk demonstrated in epidemiological studies	No or some data on possible impairment, e.g. in road safety accidentology**
LEVEL 2 **c) Moderate influence** **d) Major influence**	Pharmacodynamic influence expected	Frequent demonstration of key side effects that impair driving Rare or very rare events of certain severity*	A significant demonstration of impairment in experimental studies.	A significant increased risk is demonstrated in epidemiological studies	Data on moderate or major impairment, e.g. in road safety accidentology**

*This should be mentioned in the Patient Leaflet. A link with an additional warning in section 4.4. of the SmPC is recommended as well, similar to the link for medicines with major influence on driving (category d).

** The study of road traffic accidents with in-depth analysis of the road itself, the human behaviour and the vehicles involved.

Some challenges were highlighted with respect to the categorisation of older products compared to the newer ones. Given the difference in the evidence base of older products a distinct approach to look at two important issues was discussed. These issues are described as follows:

- *Probability of the impairing effect*.

  The calculation of frequency of events has developed over time, therefore differences can occur. However, it is emphasised that the calculation of frequency of events is only an estimate, currently based on clinical studies, which are not always available for the older products.

- *Quality of the evidence*.
  Experimental evidence for older products is often lacking. Results from epidemiological studies may be more readily available for the older products or class effects. Evidence from different sources should be given different weights.

It was recognised that none of the currently available data is absolute. There was a large amount of variability and this will not improve over time. Data that can be used to define the two groups of medicines either as having the potential to influence fitness to drive or not as presented in Table 6. There is a need to further develop the basic criteria for assessment of medicines into these two groups.

Experiences with categorizing medicines based on limited data have shown that categorization is possible. As outlined in an earlier Chapter, various European countries participating in the DRUID project have devised and categorised medicines in a number of ways for a variety of reasons with varying outcomes.

The PhVWP proposal can be considered as a first step forward to a common approach to categorisation with the aim to improve the information for patients in the Patient Leaflet. It is acknowledged by the PhVWP that at the Member States' level more activities may be undertaken to build on this framework and bring this information to the attention of patients and healthcare professionals. With this aim, national discretion is recognized with regard to:

1. The use of an alerting pictogram on the product packaging.

2. Further stratification of the number of categories of risk to a maximum of four, consistent with the current EU Guideline on Summary of Product Characteristics (SmPC).

Collaboration of DRUID experts with the PhVWP

A consensus was reached after the discussions of the DRUID WP 4 Partners with the PhVWP on how to proceed. It has been mentioned before that the proposals in this Chapter are based on input from the PhVWP on the proposals put forward by the DRUID WP4 Partners. A consultation with stakeholders, e.g. the pharmaceutical manufacturers and patient representatives, would still be necessary before a standard Patient Leaflet wording reaches a formal agreement. In the mean time collaboration with DRUID experts will be welcomed in the following areas:

1. Further elaboration of a list of undesirable effects of medicines that can impair fitness to drive.

2. Clarification of criteria for the evidence in assigning medicines to a specific level of the categorisation:
    i. Prioritisation of adverse reactions with increased influence “per se“ on driving.
    ii. Probability of the effect.
    iii. Quality of evidence.
    iv. How to take into account the difference in the evidence base of old and new products.

3. Guidance on supplementary information for patients, in support of the two levels of risk categorisation, as proposed for the Patient Leaflet.

4. Development of commitment with other EU agencies, e.g. DG Sanco, to develop a plan for ongoing activities (see 1-3 above, as well as evaluations of implementation of Member States’ activities) after the end of the DRUID-project.

Conclusions and recommendations

Input for the further development of criteria for a European categorisation system is based on the following conclusions derived from the activities in Work Package 4.

General conclusions

1. The overview of perspectives in classification systems shows the evolution in the development of the classification systems, from an effort to achieve consensus about the various categories and descriptions from a scientific perspective to efforts for informing health care professionals (e.g. Belgium, the Netherlands, Spain) to efforts for introducing warning symbols and directions for patients, as end users, in a legal framework (e.g. in France, Spain and Slovenia).

2. It has been made clear by the developments and experiences in various countries that categorisation of medicines is possible, needed and well accepted by all parties that have an interest in the safe use of medicines.

Conclusions at the level of developing criteria

1. At the level of categorising medicines it was agreed that several factors (e.g. pharmacodynamics, pharmacokinetics, pharmacovigilance data, experimental and epidemiological data, individual sensitivity, conditions of use) need to be considered for evaluating the medicines' overall potential to impair fitness to drive.

2. In circumstances where information on experimental studies or epidemiological data are lacking, the occurrence of pharmacodynamic effects resulting in undesirable effects that have the potential to impair the fitness to drive based on information in section 4.8 of the SmPC, was considered as key information for categorising some medicines.

3. The revised SmPC Guidelines (adopted in September 2009 and to be applied as from 1st of May 2010) show four descriptions of potential levels of influence on fitness to drive (a-d in section 4.7.). DRUID and the PhVWP concluded, however, that an evidence based approach supported a two tier system of warnings which may be supported by symbols or pictograms.

4. Warning levels, symbols and pictograms (in combination with a short explanation in writing) to inform patients can be developed.

Recommendations

It is clear that the establishment of criteria for a European categorisation system for medicines and driving should be based on the involvement of all relevant stakeholders. Their input is needed for developing legislation, guidelines and procedures for assigning driving impairing medicines to the appropriate category and for developing information to support health care professionals in prescribing and dispensing driving impairing medicines and patients for safely using these medicines. The following recommendations will guide further activities after the completion of the DRUID project.

1. There is a need to improve information related to effects on driving in the PIL. Information to patients who are advised to use medicines that may impair driving fitness needs to be improved by simple and patient-centred directions based on a clear categorisation system and reflected in the PIL.

2. A basic 2-tier risk categorisation system with standard wordings for the PIL is recommended for medicines without a potential influence on driving fitness (Level 1, reflective of SmPC descriptions; a) no or negligible influence or b) minor influence) and for medicines with a potential relevant influence on driving fitness (Level 2, reflective of SmPC descriptions; c) moderate influence and d) major influence).

3. Clarification of criteria for the evidence in forming the categorisations, as described as a)-d) in the SmPC (section 4.7) into the 2 levels, should be derived in a collaborative effort of DRUID experts and the members of the PhVWP of CHMP, among other partners, preferably with support of EU bodies, such as DG Sanco and DG Move.

4. The development of supplementary information for patients (e.g. warning levels, pictograms) and health care professionals (prescribing and dispensing guidelines) , in support of the categorisation system, could be guided with input provided by the DRUID project (D 4.2.1., D 4.3.1. , D 7.3.2. and D 7.4.2.) as well as by experiences in EU Member States.

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References

1. European Commission. White Paper European Transport Policy for 2010: time to decide. Office for Official Publications of the European Communities, Luxembourg, 2001.

2. Council Directive 91/439/EEC of 29 July 1991 on driving licences. Official Journal, 1991; L 237: 0001-0024.

3. Dobbs BM. Medical conditions and driving: a review of the literature (1960-2000). US Department of Transport, Washington, 2005.

4. Canadian Cardiovascular Society. Consensus Conference on assessment of the cardiac patient for fitness to drive. Can. J. Cardiol. 12 (1996) 1164-70.

5. Austroads. Assessing fitness to drive. Third edition Austroads, Sydney, 2003.

6. Council Resolution of 27 November 2003 on combating the impact of psychoactive substances use on road accidents. Official Journal C 097, 22/04/2004 P. 0001 - 0003.

7. Directorate General for Energy and Transport. Report on drugs, medicines and driving. Directorate General for Energy and Transport, European Union, Brussels, 2002.

8. Call for proposals for indirect RTD actions under the specific programme for research, technological development and demonstration: 'Integrating and strengthening the European Research Area' — Thematic priority area: 'Aeronautics and Space', 'Sustainable Energy Systems' and 'Sustainable Surface Transport' - Call identifier: FP6-2004-TREN-3. Official Journal of the European Union of 29 June 2004, C169/3.

9. Council Directive 2001/83/EEC of 6 November 2001 on the Community code relating to medicinal products for human use, Official Journal EEC L311, 2001.

10. Álvarez FJ, Del Río MC (2002) Medicinal drugs and driving: from research to clinical practice. Trends Pharmacol. Sci. 23 :441-445.

11. De Gier JJ (1998) Drugs and driving Research: Application of Results by Drug Regulatory Authorities. Hum. Psychopharmacol. Clin. Exp. 13: S133-S136.

12. Anonymous (1995) Guidelines on psychotropic drugs for the EC. Clinical investigation of medicinal products in the treatment of generalized anxiety disorder, panic disorder and obsessive-compulsive disorder. Eur. Neuropsychopharm. 5 : 151-1551.

13. Wolschrijn H, de Gier JJ, de Smet PAGM. Drugs and driving: a new categorisation system for drugs affecting psychomotor performance. Institute for drugs, safety and behaviour, University of Limburg, Maastricht, IVGV 91-24, 1991.

14. Toxicological Society of Belgium and Luxembourg asbl. Influence des médicaments sur les capacités de conduire. Toxicological Society of Belgium and Luxembourg asbl, Bruxelles, 1999.

15. Del Río MC, Alvarez FJ, González-Luque JC. Guía de prescripción farmacológica y seguridad vial [The Pharmaceutical Prescription Guidelines and Road Safety], 2nd Ed. Dirección General de Tráfico, Madrid, 2002.

16. Prévention Routière. Medicaments et aptitude à la conduite, classification des médicaments en function de leurs effets sur la capacité de conduit et le comportement au volant, implications en terme d'aptitude aux different

groups de permis de conduire, Centre d'Etudes et de Recherches en Médecine du Trafic, Annecy, France, 2000.

17. Ministère de la Santé et des Solidarités, Arrêté du 18 Juillet 2005 pris pour l´application de l´article R.5121-139 du code de la santé publique et relative à l´opposition d´un pictogramme sur le conditionnement extérieur de certain médicaments et produits. Journal Officiel de la République Française, 2 Août 2005 (SAN/P0522726A).

18. ICADTS. Prescribing and dispensing guidelines for medicinal drugs affecting driving performance, International Council on Alcohol, Drugs and Traffic Safety, 2007Available at: http://raru.adelaide.edu.au/icadts/reports/ICADTSpresguiderpt.pdf

19. de Gier JJ (2003) Medicinal Drugs: Labels and Warnings. In: Medical-Legal Aspects of drugs (Ed. Burns M) Lawyers & Judges Publishing Company Inc. Tucson Az : 279-297.

20. Stout QF and de Gier JJ. (1982) Effect van de geel-zwarte rijvaardigheidssticker [Effect of the yellow-black driving ability sticker on medicines]. Pharm Wkbld 117 : 449-55.

21. de Rooij FA en Leufkens HGM. Evaluatie-onderzoek van de Voorlichtings-campagne Geneesmiddelen en Reactievermogen [Evaluation of the public campaign on drugs and driving] Tech Report Utrecht University, Utrecht, The Netherlands, 1988.

22. Lisper B. Personal communication, 1987.

23. REAL DECRETO 1345/2007, de 11 de octobre, por el que se regula el procedimiento de autorización, registro y condiciones de dispensación de los medicamentos de uso humano fabricados industrialmente. BOE de 7 de Noviembre de 2007, pp: 45652-45698.

24. ICADTS Working group on Prescribing and Dispensing Guidelines for Medicinal Drugs Affecting Driving Performance. International Council on Alcohol, Drugs & Traffic Safety, 2001.

25. Rules on labelling of medicinal products and on the packaging leaflet (Official Journal of the Republic of Slovenia, No. 54/06 and the Medicinal Products Act (Official Journal of the republic of Slovenia, No. 31/06.

26. Orriols L, Delorme B, Gadegbeku B, Tricotel A, Contrand B et al. (2010) Prescription medicines and the risk of road traffic crashes: a French registry-based study. PloS Med 7(11): e1000366.doi:10.1371/journal.pmed.1000366.

27. Alvarez FJ. Guía Terapéutica en Atención Primaria Basada en la evidencia. Semfyc, Barcelona, 2004.

28. Regeling tot wijziging van de Regeling eisen geschiktheid 2000 met betrekking tot de geschiktheid tot het besturen van motorrijtuigen van personen met bewustzijnsstoornissen (anders dan epilepsie), ADHD (inclusief subtypen), dan wel die rijgevaarlijke geneesmiddelen gebruiken,*24 oktober 2008, Nr. CEND/HDJZ-2008/1325 sector AWW.*

29. Commentaren Medicatiebewaking (Commentary Medication Surveillance) HealthBase Foundation, Houten, The Netherlands, 2011.