Medicinal products and driving*

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1 - Introduction

The combat against road traffic accidents constitutes a major public safety concern and is a priority of the governmental authorities. Given that there are about 40,000 deaths and 1,700,000 injuries on European roads each year, the European Commission, in its 2003-2010 action program, proposed the ambitious objective of halving the number of fatalities by 2010[†]. In France, the reduction has been underway for several years. The lowest level was achieved in 2007, the sixth year of consecutive reduction, with 4,620 people killed. However, the number of injured - like the number of accidents - has increased slightly (1.1%) since 2006, showing that the mobilization must be maintained by acting on all the factors contributing to road safety.

Besides the risk associated with infrastructures and vehicle equipment, most of the risk factors are associated with behavior: excessive speed, alcohol intake, driving when tired, use of psycho-active substances and medicinal products. A great number of medicinal products have, in fact, a patent impact on the ability to drive a car. On the basis of the published data, exposure to a potentially hazardous medicinal product is observed in about 10% of road accident victims. The percentage of accidents related to medicinal product intake is, however, difficult to determine accurately. Hypnotics and anxiolytics (particularly benzodiazepines) are the drugs most frequently identified. However, few other pharmacotherapeutic classes have been studied[‡,§].

In 2003, in the context of the action program defined by the Inter-Ministerial Committee for Road Safety (CISR), The Director General of Health asked the French Agency for the Safety of Health Products (Afssaps) to consider the usefulness of classifying, within three risk levels, the medicinal products liable to impair the ability to drive, thus falling in line with the recommendations of the National Academy of Medicine[**]. In order to do so, the Afssaps has put in place a group of experts (cf. composition of this working group above) including both specialists in the various fields of pharmacology (pharmacokinetics, toxicology, pharmacovigilance) and clinicians specializing in the disciplines providing care for accident victims (neurology, ophthalmology, cardiology, legal expertise, etc.).

The proceedings enabled development of a simple device that is readily understood by everyone: a pictogram in three colors (yellow, orange, red) displayed on the outer packaging of the medicinal products involved. The device is intended to deliver practical preventive measures and thus provide concrete assistance to patients and healthcare professionals (mainly physicians and open-care pharmacists). It is to be noted that the Afssaps classification evaluates the intrinsic risk of medicinal

* By extension, this update also covers the effects of medicinal products on the ability to drive all types of vehicles (with or without a motor), use machines (including domestic and leisure use) and implement tasks requiring attention and precision.
† European Parliament resolution on the Commission communication to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions on the 'Priorities in EU road safety - Progress report and ranking of actions' (COM(2000)125 - C5-0248/2000 - 2000/2136(COS))
‡ De Gier JJ. Estimation of psychotropic drug secondary effects on vigilance. Vigilance et Transports, aspects fondamentaux, dégradation et prévention. Presse Universitaires de Lyon ed, 1995.
§ Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM. Association of road-traffic accidents with benzodiazepine use. Lancet.1998;352(9137):1331-6.
** Académie Nationale de Médecine. Rapport sur la Médecine face aux accidents de la route. June 17,2003.

products. However, the diseases for which they are administered may constitute decisive components of the ability to drive and themselves also to be taken into account.

The medicinal products liable to have an impact on the ability to drive are identified in a specific section (Effects on ability to drive and use machines) of the Summary of Product Characteristics (SPC). Initially, the expert group determined the risk level of medicinal products acting on the central nervous system and sense organs. Those products were considered, a priori, the most harmful with respect to driving. The three-level pictogram has thus been gradually applied to the corresponding proprietary medicinal products since 2005. Currently, the Afssaps has completed the risk grading of all other medicinal products associated with a risk.

However, the classification of medicinal products on the basis of their impact on the ability to drive is liable to change due to the marketing of new drug substances, emergence of new pharmacovigilance data, and the emergence of new data generated by epidemiological studies.

Accordingly, the Afssaps is contributing to a research program designed to better identify and quantify the impact of drug intake on road accidents. The program, entitled CESIR (Combination of Studies on Health and Road Safety) is based on epidemiological and pharmaco-epidemiological studies conducted in partnership with Inserm (National Institute for Health and Medical Research), Inrets (National Institute for Research on Transportation and Safety) and Cnamts (National Salaried Worker Health Insurance Organization). The program is to enable enhanced elucidation of the context of medicinal product-related accidents in France and the pertinence of the operations implemented by the Afssaps in a timeframe of one to two years.

In parallel, the work is being brought to the attention of other European Union member States with a view to initiating reflection on a common reference system.

The prevention of medicinal product-related risk in driving is based more on educational measures than on law enforcement or regulatory measures. The Afssaps is also committed to producing recommendations for a proper use, particularly through an update targeting healthcare professionals. The expert group having completed the review of all the substances associated with a driving risk, the present document constitutes an update of the document published in 2005.

2 - Review of the regulatory context

The responsibility concept

- Patient information

Information on treatments and their consequences is to be given to the patient (act dated March 4, 2002). Patients are frequently doubly informed of the risks: when prescribed by the physician and at the moment of dispensing by the pharmacist. It is admitted that the healthcare professional is not bound by a “result” obligation but in the case of information on the risks associated with treatment, professionals may be asked to demonstrate that the information was indeed delivered and understood. To prevent any discussion, the professional is advised to report that information on the ability to drive a vehicle was given to the patient in the patient's medical file and to indicate on the prescription the risk level of the medicinal product(s) involved. In all cases, the driver, independently of the information due to him/her, is directly and solely responsible for complying with the medical opinion received.

- Physical ability

The list of medical diseases incompatible with obtaining or renewing a driver's license (depending on the category of vehicle involved) is defined in a decree dated December 21, 2005. Although the effects of a medicinal product on the ability to drive and the impact of the disease under management are generally different, there are numerous cases in which they are interdependent. In the current state of the legislation, no waiver of confidentiality rules is possible, even with respect to family members. In practice, if a patient does not agree with the medical opinion, he/she may contact the department Commission to obtain an 'official' opinion on his/her ability[*].

[*] Conduire malgré une inaptitude médicale. Concours Med,2007;129:1015-7.

Information relating to the medicinal product

The marketing authorisation data state the risk constituted by medicinal products liable to impair the ability to drive. The risk is identified:

- in the Summary of Product Characteristics (SPC) in the section 4.7: 'Effects on ability to drive and use machines',
- in the user package leaflet under the item 'Drivers and machine users' where a special warning is formulated,
- on the secondary packaging of the medicinal products involved, on which, since 1999, a pictogram has been displayed. Since 2006, the pictogram has varied as a function of the level of risk associated with the medicinal product involved.

3 - Pictogram gradation by risk level

For achieving the categorisation of medicinal products, several point need to be considered:

- the strengths of the effects of a medicinal product on the ability to drive generally increase as a function of the dose, without it being possible to precisely define risk thresholds;
- there is no standardised assessment method for the car driving risk that can be applied to all medicinal products, in particular during the registration procedures,
- the epidemiological and accidentology data are few,
- individual sensitivity induces a high variability in the effects (a given dose of the same drug substance may have very different effects depending on the subject).

The qualitative classification of medicinal products using three risk levels adopted by the Afssaps was defined by practical recommendations.

- Level 1: the risk is low and largely depends on individual susceptibility; the patient is informed of the cases in which he/she should not drive in the user package leaflet (particularly when the patient has previously experienced potentially hazardous adverse reactions).

⇒ Medicinal products do not generally question the ability to drive but requiring patient information. Patients have to read the leaflet carefully before driving.

- Level 2: adverse effects on driving due to the pharmacodynamic profile predominate relative to individual susceptibility. It is appropriate to evaluate, on a case-by-case basis, whether medicinal product intake is compatible with driving. Most of the time, the medicinal product is only available on prescription and the physician will assess the patient's condition and/or response to the medicinal product. More rarely, the medicinal product may be available over the counter and thus the pharmacist's advice is of particular importance.

⇒ Medicinal products could affect the ability to drive and require medical advice, from a physician or a pharmacist, before use.

Level 3: the pharmacodynamic effects of the medicinal product make driving dangerous. With medicinal products of that type (general anesthetics, hypnotics, mydriatic eye drops, etc.), the disability is generally transient but major. Given the possibility of a carryover effect, the physician is advised to tell the patient when he/she will be able to drive again (e.g. after a period of sleep induced by a hypnotic).

⇒ Medicinal products affect the ability to drive during their use. Patients have not to drive. Before driving again, they have to seek medical advice.

As a function of the above classification, the pictogram has:

- a specific color (yellow, orange and red),
- a written indication of the risk level (1, 2 or 3),

- a written warning followed by an informative message on how to act when using the medicinal product.

The three components are systematically combined and shown on the secondary packaging of the medicinal products involved.

How to raise the question with the patient?

Each time that a medicinal product showing a pictogram is prescribed or dispensed to a patient, the patient is to be informed that intake of the medicinal product involved may impair his/her ability to drive or use machines. The warning is to be accompanied by two types of advice:

General advice

The general advice is common sense but is nonetheless worth repeating:

- Stop driving if warning signs are experienced: drowsiness, difficulty concentrating, difficulty steering, visual disorders.
- Do not take a medicinal product with which you have already experienced that type of symptom.
- Do not drink alcohol whose effects frequently potentiate those of medicinal products.
- Preferably take medicinal products liable to have an impact before going to bed.

In the event of long-term medicinal treatment, the patient is to be warned against changing the dosage or concomitantly taking a new medicinal product. In particular, the patient is to be advised against discontinuing treatment if the patient is on a treatment for a disease that, in itself, is associated with a driving risk (epilepsy, arrhythmia, depression, etc.). Attention must also be paid to identifying drug misuse or abuse and ensuring that the quantities prescribed and treatment durations do not promote misuse or abuse.

Specific advice

The treatment is chosen, when possible, according to the specific impact of each pharmacotherapeutic class (cf. next section) but also on the basis of individual risk factors:

- Age.
- Physical condition (tiredness, visual acuity).
- Psychological condition (stress, emotive state).
- Concomitant diseases and/or organ failures (kidney, liver).
- Multiple medications.
- Addiction, in particular to cannabis[*].

[*] Mura P, Kintz P, Ludes B, et al. Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study. Forensic Sci Int,2003;133:79-85.

4 - MEDICINAL PRODUCTS WITH IMPACT ON THE ABILITY TO DRIVE*

The effects of the principal pharmacotherapeutic classes liable to impair the ability to drive are described below for the attention of physicians and pharmacists. The Afssaps expert assessment was conducted using the WHO Anatomical Therapeutic Chemical (ATC) classification.

N.B.: the following description is indicative and, under no circumstances, is it a substitute for the information contained in the 'Effects on ability to drive and use machines' section of the SPC for the proprietary medicinal products involved. Moreover, special cases may exist within a given pharmacotherapeutic class (the complete list appended to article R.5121-139 of the Code of Public Health indicates the exact risk level allocated to each drug).

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DIGESTIVE TRACT AND METABOLISM

1 - Antispasmodics

- Dihexyverine and belladonna alkaloids, because of their anticholinergic effects, may induce visual accommodation disorders and behavioral disorders (irritability, confusion).

- In certain proprietary medicinal products, the antispasmodic is combined with a neuroleptic. In that case, the risk of central adverse effects, particularly drowsiness, is always to be taken into account.

- The patient is to be informed of the risk of drowsiness related to use of papaverine.

2 - Antiemetics and antinauseants

- Antiemetics pertaining to the setrons series are associated with few problems with regard to driving despite the possible occurrence of drowsiness and dizziness since they are only available on prescription and mainly used in hospitals in the context of cancer treatment.

- Antinauseants are generally used in the prevention of motion sickness. They include:
  - metopimazine which can induce drowsiness, dizziness and orthostatic hypotension. An OTC presentation is available. The user should be warned;
  - H_1 antihistamines more at marked sedation. Most are available OTC and it is important for the pharmacist to give advice when dispensing them;
  - transdermal scopolamine is probably the antinauseant with the most adverse effects on the ability to drive. Due to its anticholinergic properties, scopolamine may induce severe visual disorders (disorders and paralysis of accommodation, mydriasis).

* Taking into account data available until August 2008

3 - Antidiarrheals

- Proprietary medicinal products containing opium (paregoric) are liable to induce the characteristic adverse effects of morphine derivatives, particularly drowsiness. Abuse potential has been reported for the oral form.

- Loperamide, an opiate that only crosses the blood-brain barrier to a limited extent, is not devoid of the adverse effects of the series. However, the effects are rare and transient. The level 1 grade is particularly justified in that certain products are available OTC and thus, as a minimum, the patient should be informed of the risk.

4 - Diabetes medicinal products

The occurrence of an episode of hypoglycemia constitutes a major risk with respect to driving. In general, the risk is less associated with the specific effects of the medication than with inappropriate dosage, reduced food ration or strenuous physical exercise without dosage adjustment. Hypoglycemia is more frequent in patients on insulin therapy (more severe forms of diabetes) but may also occur with oral hypoglycemic sulfonylureas (hypoglycemia is more exceptional with thiazolidinediones, alpha-glucosidase inhibitors and biguanides). It is therefore appropriate to assess the control achieved with the treatment and to warn the patient about the factors promoting hypoglycemia. The patient should be made aware of the premonitory signs of a hypoglycemic episode and the corrective measures to be implemented (stop the vehicle, eat sugar).

CARDIOVASCULAR SYSTEM

1 - Antiarrhythmics

Antiarrhythmics, particularly those in class I of the Vaughan-Williams classification, may give rise to exacerbation or emergence of pre-existing cardiac disorders. The risk, related to the narrow therapeutic margin, calls for close monitoring by the physician. In addition, medicinal products in that class may have neurological effects such as dizziness, tremor, asthenia, drowsiness and visual disorders (blurred vision, diplopia). The patient must be informed.

2 - Nitrates

Nitrates, because of their vasodilatation properties, are able to induce orthostatic hypotension, which may be associated with dizziness, visual disorders, fainting or syncope, particularly at the start of treatment. The patient should be warned.

3 - Antihypertensives

- All antihypertensives can have an impact on driving, particularly due to their vasomotor effects. Hypotension and dizziness may occur, particularly at the start of treatment, but are generally benign and transient. After the treatment initiation or modification phase, antihypertensives are associated with few long-term problems. The patient is nonetheless to be informed of the effects and their potential potentiation by concomitant intake of other hypotensive medicinal products and alcohol.

- However, the prescription of centrally-acting antihypertensives calls for particular attention. By inhibiting the centers responsible for wakefulness and alertness, centrally-acting antihypertensives may induce sedation, which is a risk with regard to driving. It is therefore necessary to evaluate the degree to which the medication is tolerated if the patient wishes to drive.

GENITOURINARY SYSTEM MEDICINAL PRODUCTS

1 - Prolactin inhibitors

Dopaminergic agonists, indicated in the treatment of hyperprolactinemia, have the same risk profile as that of the antiparkinsonians in the same series although the doses used are lower. The physician should thus inform the patient of the possibility of suddenly falling asleep.

2 - Hormonal gynecological medicinal products

Certain hormonal compounds (progesterone, clomiphene, cyproterone acetate) may also have effects on driving (central nervous system disorders, drowsiness, visual disorders, concentration disorders) that, although minor, should be drawn to the patient's attention.

3 - Urinary antispasmodics

Due to their anticholinergic effects, urinary antispasmodics may induce accommodation disorders (mydriasis and cycloplegia).

4 - Erectile dysfunction

Erectile dysfunction medicinal products (alprostadil, sildenafil, tadalafil, vardenafil) may have an impact on the ability to drive due to their neurosensory and cardiovascular effects (dizziness, headache, etc.). The effects mainly depend on the dose used and the patient's individual susceptibility. A level 1 pictogram has been allocated to the medicinal products. However, apomorphine, because of its dopaminergic properties, is liable to induce sleepiness (level 2 pictogram).

5 - Alpha-blockers

A level 1 pictogram has been assigned to all alpha-blockers mainly because of their vasomotor effects (hypotension, dizziness).

ANTI-INFECTIVES FOR SYSTEMIC USE

1 - Tetracyclines

Among the tetracyclines, only minocycline is liable to have an impact on the ability to drive due to its numerous adverse effects: vestibular disorders, visual disorders, confusion and drowsiness. The patient's response to treatment is to be evaluated.

2 - Beta-lactams

Drivers are to be warned of the risk of dizziness and, more rarely, drowsiness associated with certain beta-lactams (ceftazidime, cefpodoxime, locarbacef, carbapenem series).

3 - Macrolides

Telithromycin calls for attentive medical surveillance given the drowsiness and myasthenia syndrome that it is liable to induce.

4 - Aminoglycosides

Cochleovestibular toxicity (balance disorders, dizziness, headache, tinnitus), inherent in aminoglycosides, constitutes the principal risk with respect to driving. Mainly promoted by a high dosage, long treatment duration or pre-existing kidney failure, the toxicity is such that the ability to drive is to be evaluated.

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5 - Quinolones

Fluoroquinolones are associated with a risk for driving due to their adverse effects on the central nervous system (in particular: dizziness, tinnitus, confusion, myoclonus, psychotic reactions, alertness disorders and motor coordination disorders). By extension, all quinolones have been classified level 2 with the exception of pipemidic acid, for which considerable therapeutic experience and reassuring data are available.

ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS

1 - Antineoplastics

Antineoplastics, because of their cytotoxic properties, have numerous adverse effects, the most patent being nausea, vomiting, headache and asthenia. Antineoplastics may also induce neurological disorders, neurosensory disorders and/or behavioral disorders which vary considerably as a function of dosage or cumulative dose administered. While the adverse effects usually occur during hospitalization, individual assessment of each patient by the physician is indispensable in order to assess the impact not only of the medicinal treatment but also of the disease on the ability to drive.

2 - Endocrine therapy

GnRH analog and antihormonal treatments are associated with a few adverse effects liable to impair the ability to drive such as drowsiness and minor visual disorders. It is necessary to adequately inform the patient of the potential adverse effects of those drugs.

Only nilutamide, which may induce more marked visual disorders and behavioral disorders, necessitates attentive patient follow-up.

3 - Immunomodulators

Interferons are associated with adverse effects that may be considered a class effect. The psychological disorders (depression, confusion, aggressiveness and suicide attempts), in particular, constitute a marked potential hazard with respect to driving necessitating attentive clinical monitoring of patients and evaluation of their ability to drive.

Reminder: the impact of the disease treated with interferons may, in certain cases, be marked (multiple sclerosis, in particular).

MUSCULOSKELETAL MEDICINAL PRODUCTS

1 - Non-steroidal anti-inflammatory drugs (NSAID), coxibs included

The shared action mechanism (inhibition of prostaglandin synthesis) gives rise to the same anti-inflammatory, analgesic, platelet aggregation inhibiting and antipyretic properties together with the same adverse effect profile. Among the adverse effects, those most likely to interfere with the ability to drive or use machines are sensory disorders and alertness and behavioral disorders. Those effects are infrequent or even rare. It is nonetheless necessary to draw the patient's attention to the potential risk of those disorders.

2 - Specific antirheumatics

Hydroxychloroquine, like all quinine derivatives, may give rise to motor neuropathy, dizziness and visual disorders. Due to the ocular toxicity of hydroxychloroquine, there is a risk of retinopathy in patients on long-term treatment. Close monitoring, particularly ophthalmologic monitoring, and regular evaluation are to be conducted for those patients.

3 - Muscle relaxants

The peripherally-acting muscle relaxants are, in most cases, neuromuscular blocking agents (curare derivatives) used as adjuvants of general anesthesia or sedation in intensive care units. Although the conditions in which muscle relaxants are administered prevent driving, the patient should abstain from driving for at least 24 hours post-dosing.

Botulinal toxin used in the management of various ocular and motor diseases and for the cosmetic treatment of facial wrinkles may induce, in particular, visual disorders, muscle weakness, dizziness and certain cardiovascular effects (arrhythmia, hypertension, syncope) that are potentially hazardous with respect to car driving. Administration must not become banal. Post-administration, attentive monitoring of the patient is required.

Centrally-acting muscle relaxants or muscle relaxants with a direct action on muscle fibers (benzodiazepines, dantrolene) are mainly associated with visual (diplopia, blurred vision, etc.), neurological (drowsiness, dizziness, seizures, etc.) and behavioral (irritability, nervousness, etc.) disorders. Their impact on the ability to drive, while not always marked, is to be the subject of evaluation and attentive monitoring. Some products are available OTC (mephenesin).

NERVOUS SYSTEM

1 - Anesthetics

- The impact of local anesthetics varies depending on the mode of adminsitration. Thus, the use of local anesthetics for sensory block in local and regional anesthesia contra-indicates driving, if only because of the sensory-motor disorders induced. Assessment of recovery of the ability to drive is necessary (level 3). More generally, the use of local anesthetics in everyday practice (in particular in odontology) does not call for the physician systematically advising the patient against driving, but does necessitate individual assessment of the impact by the physician (level 2).

- After general anesthesia, vehicle driving is to be advised against at least on the day of the procedure. The recovery of the ability to drive is to be systematically assessed by a physician, who is to use assessment scales to do so.

2 - Analgesics

Two pharmacological classes are involved:

- Non-opioid analgesics: NSAID used at analgesic or antipyretic dosages may be associated with a driving risk. However, it is slight and infrequent (dizziness and visual disorders).

- Opioid analgesics, including drugs such as dextropropoxyphene. Opioid analgesics induce marked sedation and behavioral disorders that may prevent the patient becoming aware of the impairment in his/her ability to drive and thus lead him/her to take ill-considered risks. Moreover, there is great between-individual variability in sensitivity to that type of drug. The ability to drive is to be the subject of an attentive medical assessment, in particular during the treatment initiation phase.

Codeine at low dosages (codeine base dose less than 20 mg per unit) is nonetheless associated with less marked effects. The patient should simply be informed.

3 - Anti-migraine medicinal products

All serotonin 5-HT_1 receptor agonists (triptans) and some other anti-migraine medicinal products (pizotifen, oxetorone, flunarizine and metoclopramide in combination with aspirin) frequently induce sedation and dizziness, necessitating individual evaluation of the patient's.

4 - Anticonvulsants

The principal risk associated with anticonvulsant medicinal products resides in sedation, enebriated sensations and psychomotor retardation. But other potentially hazardous effects with respect to driving are also frequent: visual disorders, dizziness, ataxia and behavioral disorders (irritability, agitation, amnesia, apathy, depression, mental confusion). Medical evaluation on a case-by-case basis is indispensable. The evaluation is to take into account both the risk related to the disease itself (epileptic seizure) and the risk related to the drug. Driving is generally not possible at the start of treatment, but may become possible when the patient's disease has been satisfactorily controlled.

Similarly, any change in medicinal treatment is to be particularly closely monitored, particularly the addition of a second anti-epileptic (due to the risk of interaction between most of the drugs in the class).

5 - Antiparkinsonians

The adverse effects on driving, common to all the antiparkinsonians, consist in sedation and behavioral disorders (sleep disorders, hallucinations, agitation, mental confusion, delirium, psychotic episode, psychomotor excitation). Case-by-case assessment is required, particularly during the treatment initiation phase. The assessment is particularly important in that Parkinson's disease may in itself have an impact on the patient's psychomotor and cognitive abilities. While amantadine and selegiline have less marked effects, attention is drawn to levodopa and all dopaminergic agonists, since they can induce episodes of abrupt-onset sleep without premonitory signs and are thus extremely dangerous for drivers. The frequency of the adverse effects seems greater with certain recent agonists such as ropinirole and pramipexole.
Patients should be warned at medicinal treatment initiation. In the event of drowsiness, if possible, the dosage is to be reduced. If not, patients already having presented with symptoms of drowsiness are to be formally advised against driving.

6 - Neuroleptics and antipsychotics

Oral forms

Parenteral forms

The effects of neuroleptics liable to compromise the ability to drive are:

- marked sedation, particularly at treatment initiation,
- visual disorders (blurred vision, accommodation disorders, oculogyric crises, etc.),
- behavioral disorders (aggressiveness, confusion),
- deterioration of cognitive function,
- extrapyramidal syndrome,
- motor disorders (mainly tardive dyskinesia).

It should be noted that treatment discontinuation or dosage reduction may induce impairment of performance that may be markedly more prejudicial than the impairment due to the adverse effects.
Generally speaking, the greatest caution is recommended with respect to the use of neuroleptics, particularly since the adverse effects with regard to driving vary as a function of the chemical class, dosage and administration route -> level 2 pictogram for oral forms and level 3 pictogram for parenteral forms (except sustained-release forms).

7 - Anxiolytics

Oral forms

All anxiolytic treatments are hazardous for driving. Particular attention is to be paid to benzodiazepines, the class of drugs most frequently used and the class reported to have been taken most frequently by drivers causing accidents.
The impact on the ability to drive is mainly due to:

- drowsiness,

- psychomotor retardation (decrease in the ability to respond to urgent situations, increase in the reaction time to visual and auditory stimuli, impaired coordination and control of movements, etc.).

All of the above effects are potentiated by concomitant alcohol intake or concomitant intake of drugs inducing central nervous system depression (opioids, neuroleptics, antihistamines, antidepressants, sedatives, other benzodiazepines, hypnotics, anticonvulsants, muscle relaxants, phenobarbital, centrally-acting antihypertensives).

Parenteral forms and high-dose forms

Moreover, with benzodiazepines and related drugs, effects liable to induce risk behavior may occur (mood disorders, disinhibition). Benzodiazepines are associated with a potential for dependence and abuse.

The decision to prescribe an anxiolytic for a patient liable to drive must therefore be carefully weighed. Parenteral forms and high doses are incompatible with driving -> level 2 pictogram for the oral forms and level 3 pictogram for most of the parenteral forms and high-dose forms.

8 - Hypnotics

As is the case for anxiolytics, the most frequently used drugs are benzodiazepines or similar drugs. Since the objective of those drugs is to induce sleep, it is clear that driving post-intake is to be proscribed. Moreover, residual drowsiness may be present the next day and have an impact on the ability to drive or implement precise tasks during the day. The carryover effect depends on the pharmacokinetic properties of the drug and also on the patient's individual susceptibility and his/her quality of sleep (carefully check that the patient has slept long enough). The patient is to be advised against driving for as long as drowsiness persists. An assessment of the response as of the initial intakes is indispensable (the treatment duration prescribed is not normally to exceed 4 weeks). Hypnotics may induce the same effects (mood disorders, disinhibition) as anxiolytics. Hypnotics are associated with a potential for dependence and abuse.

9 - Antidepressants

Irrespective of type, all antidepressants may induce adverse effects with respect to driving: drowsiness, behavioral disorders (anxiety, agitation, hallucinations, confusion, manic episodes, suicide risk, reactivation of delirium, etc.). The drowsiness is much less marked with serotonin reuptake inhibitors and monoamine oxidase reuptake inhibitors. Imipramine antidepressants can, in addition, induce disorders related to their anticholinergic effects (visual disorders, cardiac disorders). Within a given chemical series, there may sometimes be marked differences. For instance, among the imipramine derivatives, clomipramine induces significantly less drowsiness than amitriptyline. Usually, the adverse effects are more marked at treatment initiation and, in many cases, the patient will recover his/her ability to drive after one or two weeks of treatment. Case-by-case assessment of the response to treatment and any adverse effects is therefore of fundamental importance. The physician should also be attentive to treatment failure situations since depression may, in itself, have an impact on the ability to drive (confusion, psychomotor retardation, cognitive deficiency, suicidal behavior, etc.).

10 - Other central nervous system medicinal products

Various medicinal products may also have an impact on the ability to drive and generally require individual assessment:

- stimulants and psychostimulants,
- Alzheimer's disease medicinal products,
- withdrawal medicinal products for smokers, alcoholics and patients with opioid dependency,
- anti-dizziness medicinal products.

RESPIRATORY SYSTEM

1 - Nasal decongestants

Products for local use are subject to weak systemic absorption but the possibility of a sedative effect liable to impair the ability to drive cannot be discounted.

Medicinal products for systemic administration frequently contain an antihistamine, antiseptic or anti-inflammatory. Level 1 has been allocated to all those combinations except those containing a first-generation antihistamine (level 2) or hypnotic (level 3).

2 - Cough and cold medicinal products

The driving risk may be associated with the drug substance but also with alcohol, which is frequently included in the excipient composition. Thus, patients are to be informed of the risks with regard to driving associated with all medicinal products that, at maximum dosage, result in intake of more than 3 g of alcohol daily (level 1). Some medicinal products, in addition to the alcohol content, include a drug substance liable to impair the ability to drive. Such products are classified in level 2 or level 3.

Referring only to the hazardousness specific to the drug substances:

- most antitussives are only associated with a relatively small risk with respect to driving. Opium alkaloids such as codeine, pholcodine and dextromethorphan, and other drug substances may induce sedation and dizziness without however compromising driving. The manifestations are rare at usual antitussive dosages.

- antitussives, expectorants and cold medicinal products which include among their drug substances an H_1 antihistamine are the medications most likely to impair driving due to their numerous effects on the central nervous system, such as drowsiness, visual disorders (blurred vision, mydriasis, accommodation disorders), tachycardia, irritability, etc. The effects are more marked when the drug substances used in the preparation include first-generation antihistamines. The fact that many such products are available without prescription provides the rationale for the pharmacist giving advice.

It is to be noted that several such products may give rise to excessive consumption.

3 - Systemic H_1-antihistamines used as anti-allergy medicinal products:

- Second-generation antihistamines may induce drowsiness and psychomotor retardation. The effects are generally mild and infrequent. However, it is appropriate to take them into account for the initial prescription.

The first-generation antihistamines are characterized by a more marked sedative effect at usual dosages. The risk of drowsiness varies depending on the patient. Drowsiness may be accompanied by visual disorders (blurred vision, mydriasis, accommodation disorders), behavioral disorders (hallucinations), dizziness, paresthesia and possibly orthostatic hypotension. The adverse effects with respect to driving may persist over a variable duration. Most of the products are available OTC. Patients who wish to drive during allergy treatment should at least be advised of the risk by the pharmacist.

OPHTHALMOLOGIC MEDICINAL PRODUCTS

Generally speaking, the patient should be advised that local administration of ophthalmologic medicinal products (particularly in ointment form) may induce blurred vision temporarily interfering with driving.

In increasing order of hazardousness, the following are to be distinguished:

- Anti-infectives and anti-inflammatories which, although liable to induce transient ocular irritation, only slightly disturb vision.
- The same applies to the anti-allergy medicinal products that, in the event of systemic absorption, may have an impact on the central nervous system via drug interactions and induce drowsiness.

Instillation of antiglaucoma medicinal products may induce visual disorders of variable severity (mydriasis, with the exception of the parasympathomimetics, which induce myosis), cardiac disorders and alertness disorders (drowsiness). Monitoring is strongly recommended, particularly for the elderly, who are frequently on multiple medicinal products.

- Parasympathomimetics used as antiglaucoma medicinal products (pilocarpine, carbachol, acetylcholine, etc.) may induce accommodation spasm. Their action duration is variable. Myosis may compromise driving, particularly driving at night.

- The principal risk associated with sympathomimetics used as decongestants (low doses) consists in their misuse: used at excessively high doses, they induce mydriasis but also an increase in blood pressure and cardiac rhythm disorders. The risks are particularly to be taken into consideration since most of the products are available without prescription.

- Mydriatics and cycloplegics induce mydriasis and paralysis of accommodation, respectively. The duration may range from a few hours to several days. Behavioral disorders may also occur. Driving is to be formally proscribed throughout the duration of mydriasis, particularly since the latter is usually accompanied by photophobia.

5 - CONCLUSIONS

Out of over 9,000 proprietary medicinal products currently marketed in France, about 3,000 have effects that are liable to impact the ability to drive. Given the large number and diversity of the drugs involved, it is important for healthcare professionals prescribing, dispensing or administering medicinal products to patients to be able to identify the most hazardous drugs rapidly.

Overall, medicinal products incompatible with driving only account for about one drug in fifty. Moreover, it is relatively easy to focus attention on the principal pharmacotherapeutic classes involved since they essentially consist in hypnotics, anxiolytics, neuroleptics, anesthetics, neuromuscular blocking agents and mydriatic eye drops (cf. appendix).

In future, the three-risk level pictogram as per the Afssaps classification should therefore alert the patient while promoting dialogue with healthcare professionals with regard to widely used proprietary medicinal products such as analgesics, systemic allergy medications, cough and cold medications and motion sickness medications.

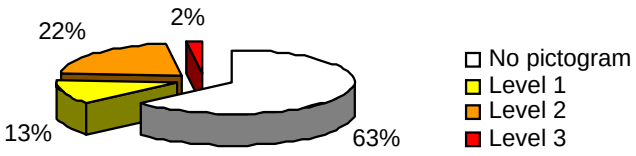
The dialogue is also to be promoted during initiation of all long-term treatments which have an impact on the ability to drive such as antidepressant, anticonvulsant, antiparkinsonian, antidiabetic, antihypertensive and anti-glaucomatous treatments. The ultimate objective is to prevent a potential risk for the patient and for other road users while limiting the exclusion of patients who have to take hazardous medicinal treatment daily.

6 - APPENDIX

Quantitatively, the Afssaps' risk gradation is distributed as follows:

Therapeutic class (ATC)	Level 1	Level 2	Level 3
Digestive tract and metabolism (A)	**80**	**196**	**1**
Cardiovascular system (C)	**348**	**28**	**0**
Genitourinary system (G)	**80**	**21**	**0**
Anti-infectives for systemic use (J)	**82**	**159**	**0**
Antineoplastics and immunomodulating agents (L)	**39**	**120**	**0**
Musculoskeletal system (M)	**153**	**43**	**14**
Nervous system (N)	**90**	**902**	**157**
Respiratory system (R)	**128**	**75**	**1**
Ophthalmology (S)	**120**	**29**	**14**

General distribution of the risk levels ->



The list below is indicative. It does not supersede the appendix to the decree dated August 8, 2008, enacting article R. 5121-139 of the Code of Public Health, which states the exhaustive list of all the drug substances with effects on the ability to drive or use machines, as per the ATC classification, and the risk level allocated to them.

When a medicinal product contains several active substances with different risk levels, the highest level pictogram is applied.

Particular case: when a medicinal product contains alcohol as an excipient:
- the level 1 pictogram is justified for medicinal products for which the amount of alcohol contained in the maximum daily dosage exceeds 3 g,
- the level 2 pictogram is justified for medicinal products for which the amount of alcohol contained in the maximum daily dosage exceeds 3 g and which contain another substance liable to have an effect on driving,

Aceclofenac	Level 1
Acepromazine (in combination)	Level 3
Aceprometazine (in combination)	Level 3
Acetylcholine	Level 2
Acitretin	Level 1
Aldesleukin	Level 2
Alemtuzumab	Level 2
Alfentanil	Level 3
Alfuzosin	Level 1
Alimemazine	Level 2
Alminoprofen	Level 1
Almotriptan	Level 2
Alprazolam	Level 2
Alprostadil	Level 1
Amantadine	Level 1
Amikacin	Level 2
Amisulpride	Level 2 (oral forms) Level 3 (parenteral forms)
Amitriptyline	Level 2
Amlodipine	Level 1
Amodiaquine	Level 1
Amoxapine	Level 2
Anastrozole	Level 1
Apomorphine	Level 2
Apraclonidine	Level 1
Aprindine	Level 1
Articaine	Level 2
Atracurium	Level 3
Atropine	Level 2 (used as antispasmodic) Level 3 (used as mydriatic)
Azelastine	Level 1

Baclofen	Level 2
Benazepril	Level 1
Benfluorex	Level 1
Bexarotene	Level 2
Bimatoprost	Level 1
Biperiden	Level 2
Bortezomid	Level 2
Bosentan	Level 1
Botulinum toxin	Level 2
Brimonidine	Level 1
Brinzolamide	Level 1
Bromazepam	Level 2
Bromides	Level 1
Bromocriptine	Level 2
Bromolactobionate	Level 1
Brompheniramine	Level 2
Brotizolam	Level 3
Buclizine	Level 2
Bupivacaine	Level 2 (used in dental anesthesia) Level 3 (used in regional/local anesthesia)
Buprenorphine	Level 2
Bupropion	Level 2
Buserelin	Level 1
Buspirone	Level 1
Butobarbital	Level 3
Butylscopolamine	Level 2
Cabergoline	Level 2
Calcitonin (salmon synthetic)	Level 1
Candesartan	Level 1
Capecitabine	Level 2
Captodiame	Level 1
Captopril	Level 1
Carbachol	Level 2
Carbamazepine	Level 2
Carbinoxamine	Level 2
Carbutamide	Level 2
Carpipramine	Level 2
Carteolol	Level 1 (used in ophthalmology)
Cefpodoxime	Level 1
Ceftazidime	Level 1
Celecoxib	Level 1
Cetirizine	Level 1
Chloramphenicol	Level 1 (used in ophthalmology)
Chlordiazepoxide	Level 2
Chloroquine	Level 1

Chlorphenamine	Level 2
Chlorphenoxamine	Level 2
Chlorpromazine	Level 2 (oral forms) Level 3 (parenteral forms)
Chlortetracycline	Level 1
Cibenzoline	Level 1
Cilazapril	Level 1
Ciprofloxacin	Level 1 (used in ophthalmology) Level 2 (systemic use)
Cisatracurium	Level 3
Cisplatin	Level 2
Citalopram	Level 2
Cladribine	Level 2
Clobazam	Level 2
Clofazimine	Level 2
Clomifene	Level 1
Clomipramine	Level 2
Clonazepam	Level 2 (oral forms) Level 3 (parenteral forms)
Clonidine	Level 2
Clorazepate	Level 2 (oral forms) Level 3 (parenteral forms and 20 mg and more oral forms)
Clorazepate *(in combination)*	Level 3
Clotiazepam	Level 2
Clozapine	Level 2
Codeine	Level 1 (codeine-base dose < 20 mg) Level 2 (codeine-base dose for codeine doses > 20 mg)
Cromoglicic acid	Level 1
Cyamemazine	Level 2 (oral forms) Level 3 (parenteral forms)
Cyclopentolate	Level 3
Cyproheptadine	Level 2
Cyproterone	Level 1
Cytarabine	Level 2
Dacarbazine	Level 2
Dactinomycin	Level 2
Dalfopristin	Level 1
Dantrolene	Level 2
Daunorubicin	Level 2
Deferasirox	Level 2
Deferoxamine	Level 2
Desflurane	Level 3
Desipramine	Level 2
Desloratadine	Level 1
Dexamethasone	Level 1 (used in ophthalmology)

Dexchlorpheniramine	Level 2
Dexibuprofen	Level 1
Dexketoprofen	Level 1
Dextromethorphan	Level 1
Dextromoramide	Level 2
Dextropropoxyphene	Level 2
Diazepam	Level 2 (oral forms) Level 3 (parenteral forms and 10 mg oral forms)
Diclofenac	Level 1 (systemic use)
Diethylcarbamazine	Level 1
Dihexyverine	Level 2
Dihydrocodeine	Level 2
Dimenhydrinate	Level 2
Diphenhydramine	Level 2
Dipivefrine	Level 1
Disopyramide	Level 1
Disulfiram	Level 2
Dolasetron	Level 1
Donepezil	Level 2
Dorzolamide	Level 1
Dosulepin	Level 2
Doxazosin	Level 1
Doxepin	Level 2
Doxorubicin	Level 2
Doxylamine	Level 3
Droperidol	Level 3
Efavirenz	Level 2
Eletriptan	Level 2
Enalapril	Level 1
Encephalitis vaccines : encephalitis, tick borne, inactivated, whole virus	Level 1
Enflurane	Level 3
Enoxacin	Level 2
Entacapone	Level 2
Eprosartan	Level 1
Ergotamine	Level 1
Ertapenem	Level 1
Escitalopram	Level 2
Estazolam	Level 3
Ethambutol	Level 2
Ethanol	Level 3
Ethosuximide	Level 2
Ethylmorphine	Level 1
Etifoxine	Level 1
Etodolac	Level 1

Etomidate	Level 3
Etoposide	Level 2
Exemestane	Level 1
Felbamate	Level 2
Felodipine	Level 1
Fenoprofen	Level 1
Fentanyl	Level 3 (used in anesthesia) Level 2 (as transdermal analgesic) Level 3 (as transmucosal analgesic and iontophoretic)
Flecainide	Level 1
Floctafenine	Level 1
Fluanisone	Level 2 (oral forms) Level 3 (parenteral forms)
Fludarabine	Level 2
Flumazenil	Level 3
Flumequine	Level 2
Flunarizine	Level 2
Flunitrazepam	Level 3
Fluorescein	Level 1 (parenteral forms)
Fluoxetine	Level 2
Flupentixol	Level 2 (oral forms) Level 3 (parenteral forms except SR forms)
Fluphenazine	Level 2 (oral forms) Level 3 (parenteral forms)
Flurazepam	Level 3
Flurbiprofen	Level 1
Fluvoxamine	Level 2
Fomepizole	Level 2
Fosinopril	Level 1
Fosphenytoin	Level 2
Framycetin	Level 1 (used in ophthalmology)
Frovatriptan	Level 2
Gabapentin	Level 2
Galantamine	Level 2
Ganciclovir	Level 2
Gemcitabine	Level 2
Gentamicin	Level 2 (systemic use) Level 1 (used in ophthalmology)
Glibenclamide	Level 2
Glibornuride	Level 2
Gliclazide	Level 2
Glimepiride	Level 2
Glipizide	Level 2
Granisetron	Level 1
Guanfacine	Level 2

Haloperidol	Level 2 (oral forms) Level 3 (parenteral forms except sustained-released forms)
Halothane	Level 3
Homatropine	Level 3
Hydromorphone	Level 2
Hydroquinidine	Level 1
Hydroxychloroquine	Level 2
Hydroxyzine	Level 2
Ibuprofen	Level 1
Ifosfamide	Level 2
Imatinib	Level 2
Imidapril	Level 1
Imipramine	Level 2
Indocyanine	Level 1
Indometacin	Level 1
Insulin	Level 2
Interferon	Level 2
Iodixanol	Level 1
Iproniazide	Level 2
Irbesartan	Level 1
Irinotecan	Level 2
Isoflurane	Level 3
Isosorbide dinitrate	Level 1
Isosorbide mononitrate	Level 1
Isothipendyl	Level 2
Isotretinoin	Level 1
Isradipine	Level 1
Ivabradine	Level 2
Ketamine	Level 3
Ketoprofen	Level 1
Ketotifen	Level 2 (oral forms) Level 1 (used in ophthalmology)
Lamotrigine	Level 2
Latanoprost	Level 1
Lenalidomide	Level 2
Letrozole	Level 1
Leuprorelin	Level 1
Levetiracetam	Level 2
Levobunolol	Level 1
Levocetirizine	Level 1
Levodopa	Level 2
Levofloxacin	Level 2
Levomepromazine	Level 2 (oral forms) Level 3 (parenteral forms)
Lidocaine	Level 2 (parenteral forms)

Linezolid	Level 2
Lisinopril	Level 1
Lisuride	Level 2
Lithium	Level 2
Loflazepate	Level 2
Lomefloxacin	Level 2
Loperamide	Level 1
Loprazolam	Level 3
Loracarbef	Level 1
Loratadine	Level 1
Lorazepam	Level 2 Level 3 (2,5 mg forms)
Lormetazepam	Level 3
Loxapine	Level 2 (oral forms) Level 3 (parenteral forms)
Manidipine	Level 1
Maprotiline	Level 2
Meclozine	Level 2
Medazepam	Level 2
Mefenamic acid	Level 1
Mefloquine	Level 1
Meloxicam	Level 1
Memantine	Level 2
Meningococcus C antigen	Level 1
Mephenesin	Level 2
Mepivacaine	Level 2
Meprobamate	Level 2 (oral forms) Level 3 (parenteral forms)
Meprobamate (in combination)	Level 3 in combination with acepromethazine Level 2 in combination with other substances
Mepyramine	Level 2
Mequitazine	Level 2
Meropenem	Level 1
Methadone	Level 2
Methocarbamol	Level 2
Methyldopa	Level 2
Methylphenidate	Level 2
Metipranolol	Level 1
Metoclopramide	Level 2
Metopimazine	Level 2
Metronidazole	Level 1
Metyrapone	Level 1
Mexiletine	Level 1
Mianserin	Level 2
Midazolam	Level 3

Midodrine	Level 1
Milnacipran	Level 2
Minocycline	Level 2
Mirtazapine	Level 2
Mitotane	Level 2
Mivacurium	Level 3
Mizolastine	Level 2
Moclobemide	Level 2
Moexipril	Level 1
Morniflumate	Level 1
Morphine	Level 2
Moxifloxacin	Level 2
Moxonidine	Level 2
Nabumetone	Level 1
Nalbufine	Level 2
Nalidixic acid	Level 2
Nalorphine	Level 3
Naltrexone	Level 2
Naphazoline	Level 2 (used in ophthalmology)
Naproxen	Level 1
Naratriptan	Level 2
Nateglinide	Level 2
Nefopam	Level 2
Neomycin	Level 1 (used in ophthalmology)
Netilmicin	Level 2
Niaprazine	Level 3
Niflumic acid	Level 1
Nilutamide	Level 2
Nimesulide	Level 1
Nitrazepam	Level 3
Nitrendipine	Level 1
Nitrous oxide	Level 2
Nordazepam	Level 2 Level 3 (15-mg forms)
Norfloxacin	Level 2
Noscapine	Level 1
Ofloxacin	Level 2
Olanzapine	Level 2 (oral forms) Level 3 (parenteral forms)
Olmesartan medoxomil	Level 1
Olopatadine	Level 1
Ondansetron	Level 1
Opipramol	Level 2
Opium	Level 2
Ornidazole	Level 1

Oxatomide	Level 2
Oxazepam	Level 2 Level 3 (50 mg forms)
Oxcarbazepine	Level 2
Oxedrine	Level 2
Oxetorone	Level 2
Oxitriptan	Level 2
Oxomemazine	Level 2
Oxybutynin	Level 2
Oxycodone	Level 2
Oxytetracycline	Level 1 (used in ophthalmology)
Paclitaxel	Level 2
Pamidronic acid	Level 2
Pancuronium	Level 3
Papaverine	Level 1
Parecoxib	Level 1
Paroxetine	Level 2
Pefloxacin	Level 2
Peginterferon alfa-2a	Level 2
Peginterferon alfa-2b	Level 2
Pemetrexed	Level 2
Penfluridol	Level 2
Pentaerithrityl tetranitrate	Level 1
Pentazocine	Level 2
Pentostatin	Level 2
Pentoxyverine	Level 1
Pergolide	Level 2
Periciazine	Level 2
Perindopril	Level 1
Perphenazine	Level 3
Pethidine	Level 2
Pheniramine	Level 2
Phenobarbital	Level 2
Phenylbutazone	Level 1
Phenylephrine	Level 3 (used as a mydriatic) Level 2 (others uses in ophtalmology)
Phenyltoloxamine	Level 1
Phenytoin	Level 2
Pholcodine	Level 1
Pilocarpine	Level 2 (used in ophthalmology)
Pimethixene	Level 2
Pimozide	Level 2
Pipamperone	Level 2
Pipemidic acid	Level 1

Pipotiazine	Level 2 (oral forms) Level 3 (parenteral forms)
Piracetam	Level 2
Piribedil	Level 2
Piroxicam	Level 1
Pizotifen	Level 2
Polymyxin B	Level 1 (used in ophthalmology)
Posaconazole	Level 2
Pralidoxime	Level 1
Pramipexole	Level 2
Prazepam	Level 2 Level 3 (40 mg forms)
Praziquantel	Level 1
Prazosin	Level 1
Pregabalin	Level 2
Primidone	Level 2
Procaine	Level 2
Progabide	Level 2
Progesterone	Level 1 (oral or vaginal forms)
Promethazine	Level 2 (systemic use)
Propafenone	Level 1
Propofol	Level 3
Quinagolide	Level 2
Quinapril	Level 1
Quinine	Level 1
Quinupristin	Level 1
Raltitrexed	Level 2
Ramipril	Level 1
Remifentanil	Level 3
Repaglinide	Level 2
Ribavirin	Level 1
Rifamycin	Level 1
Rilmenidine	Level 2
Riluzole	Level 1
Rimexolone	Level 1
Risperidone	Level 2
Ritonavir	Level 1
Rivastigmine	Level 2
Rizatriptan	Level 2
Rocuronium	Level 3
Ropinirole	Level 2
Ropivacaine	Level 2
Roxithromycin	Level 1
Scopolamine	Level 2
Secnidazole	Level 1

Selegiline	Level 1
Sertindole	Level 2
Sertraline	Level 2
Sevoflurane	Level 3
Sibutramine	Level 2
Sildenafil	Level 1
Solifenacin	Level 2
Sufentanil	Level 3
Sulindac	Level 1
Sulpiride	Level 2 (oral forms) Level 3 (parenteral forms)
Sultopride	Level 2 (oral forms) Level 3 (parenteral forms)
Sumatriptan	Level 2
Suxamethonium	Level 3
Tacrolimus	Level 2
Tadalafil	Level 1
Tamoxifen	Level 1
Tamsulosin	Level 1
Tegafur	Level 2
Teicoplanin	Level 1
Telithromycin	Level 2
Telmisartan	Level 1
Temazepam	Level 3
Temozolomide	Level 2
Tenoxicam	Level 1
Terazosin	Level 1
Teriparatide	Level 1
Tetrabenazine	Level 2
Tetrazepam	Level 2
Tetryzoline	Level 2
Thiopental	Level 3
Thioproperazine	Level 2
Thioridazine	Level 2
Tiagabine	Level 2
Tianeptine	Level 2
Tiapride	Level 2 (oral forms) Level 3 (parenteral forms)
Tiaprofenic acid	Level 1
Timolol	Level 1 (used in ophthalmology)
Tinidazole	Level 1
Tobramycin	Level 1 (used in ophthalmology) Level 2 (systemic use)
Tofisopam	Level 2
Tolcapone	Level 2

Toloxatone	Level 2
Tolterodine	Level 2
Topiramate	Level 2
Tramadol	Level 2
Trandolapril	Level 1
Tranexamic acid	Level 1
Travoprost	Level 1
Tretinoin	Level 2
Triazolam	Level 3
Triclabendazole	Level 1
Trifluoperazine	Level 2
Trihexyphenidyl	Level 2
Trimipramine	Level 2
Trinitrate	Level 1
Triprolidine	Level 2
Triptorelin	Level 1
Tropatepine	Level 2
Tropicamide	Level 3
Tropisetron	Level 1
Trospium	Level 2
Urapidil	Level 1
Valganciclovir	Level 2
Valproic acid	Level 2
Valpromide	Level 2
Valsartan	Level 1
Vardenafil	Level 1
Varenicline	Level 1
Vecuronium	Level 3
Venlafaxine	Level 2
Veraliprid	Level 2
Vigabatrin	Level 2
Viloxazine	Level 2
Vinblastine	Level 2
Vincristine	Level 2
Vindesine	Level 2
Voriconazole	Level 2
Zofenopril	Level 1
Zolmitriptan	Level 2
Zolpidem	Level 3
Zonisamide	Level 2
Zopiclone	Level 3
Zuclopenthixol	Level 2 (oral forms) Level 3 (parenteral forms except sustained-released forms)