

The G-Standaard: structure, safety assessment and decision support

1. Structure

1.1 Hierarchy

The (un)licensed medicines in the G-Standaard are identified by a fixed number of identifying characteristics. The identifying characteristics are recorded on the level of the trade product; subsets of the different characteristics form a hierarchical structure. The different levels are generated automatically, which prevents duplication. The backbone of the hierarchical structure is established as a standard of the Dutch normalisation institute.

The main hierarchical levels are (ranges from most detailed to less detailed):

Consumer article

This is the level of the package that is dispensed to the patient, and it includes for example package size and registration number.

The consumer article consists of a unique numeric code, a consumer article name and the identifying characteristics.

Trade product

This is the level of the trade name. It is identified by more than 30 characteristics, but does not include package size and registration number.

The trade product consists of a unique numeric code, a trade product name and the identifying characteristics.

Prescription level

The prescription level is the level that can be used for generic prescription. It consists of a limited subset of the characteristics of the trade product. These are:

- active ingredient(s), including the salt
- strength (including the unit of the dose form)
- dose form
- route of administration.
- container type, such as vial or ampoule
- quantity per container type, such as 2 ml
- devices, such as babyhaler
- identifying additives, for example preservatives
- additional features such as "XE" in timolol eye drops
- length and width of a bandage
- size of an IUD

The prescription level consists of a unique numeric code, a prescription name (in the fixed order: drug name – dose form – strength - additional information) and the identifying characteristics.

Pharmaceutical level

The pharmaceutical level describes the pharmaceutical characteristics of the drug. These are:

- active ingredient(s), including the salt
- strength (including the unit of the dose form)
- dose form

- route of administration.

The pharmaceutical level consists of a unique numeric code, a generic name (in the fixed order: drug name – dose form – strength) and the identifying characteristics.

Drug name

The less detailed level is the level of the active moiety (e.g. ‘paroxetine’). The active moiety can have different salt forms or water of hydration. The salts and water of hydration are separate names, which are hierarchical ‘children’ of the active moiety (e.g. ‘paroxetine hydrochloride 0.5-water’, ‘paroxetine mesilate’).

1.2 Content of the identifying characteristics

The identifying characteristics are recorded on the level of the trade product. The characteristics are filled based on the SPC data of the product.

1.3 Usage of international terminologies and classifications

The characteristics are based as much as possible on international standards.

- the drug name is based on the INN
- the dose forms and routes of administration are based on the standard terms of the European Pharmacopeia Commission.
- the units are based on the SI-system
- ATC and DDD of the WHO are included, and it is linked on the pharmaceutical level.
- at this moment, the Royal Dutch Association for the Advancement of Pharmacy is involved in a project to improve the structure of the pharmaceutical terminology of SNOMED CT. The proposed improved structure of SNOMED will fit nearly completely with the pharmaceutical level of the G-Standaard, so in future a mapping can be made
- at this moment there are joined forces with GS1, to include their identification code EAN (or GTIN) in the G-Standaard and vice versa.

2. Decision support

2.1 Interactions

Levels of relevance

The interactions are divided in several levels of relevance. These levels are designated with the following codes:

- Yes / Yes (yes, there is an interaction and yes, action is needed)
- No / Yes (no interaction, but action is necessary nevertheless).
- Yes / No (yes, there is an interaction, no, action is not necessary or not possible)
- No / No (no interaction, no action is needed)

The yes/yes and no/yes interaction appear as an alert on the screen of the healthcare professional during prescribing and before dispensing.

The yes/no and no/no interactions can be consulted in the system or can be printed on a list at the end of the day.

In addition, the interaction module has a number of refinements, such as

- reporting in case of stopping the medication
- relevant period which should be monitored after discontinuation of a medication, for instance, in case of enzyme induction or irreversible blockade of enzyme (such as MAO inhibitors with SSRIs).

Practical guidelines

The alerts that appear on the screen of the healthcare professional, are accompanied with practical guidelines how to deal with the alert. Furthermore, some information about the mechanism and the consequences of the interaction are included.

Transparency of evidence

All interactions are based on original literature and the information in the handbooks of Stockley and Hansten&Horn. The literature and the practical guideline are assessed by an expert group with day to day clinical experience. Each interaction is assigned with an alphanumeric code, to indicate the level of evidence and the severity of the consequences of the interaction.

The literature and alphanumeric code is available for the healthcare professional in a separate datasheet.

The method is published in: Van Roon E et al. Clinical relevance of drug-drug interactions: a structured assessment procedure. *Drug Safety* 2005;28(12):1131-9.

Content

In addition to the regular interactions, interactions for oncolytics, HIV-medication and anticoagulants have also been assessed.

2.2 Contra-indications

The contra-indications have the same structure as the interactions, including the different levels of relevance, practical guidelines and transparency of evidence.

The module Contra-indications includes several types of contra-indications:

- diseases, like diabetes mellitus
- renal impairment
- pregnancy and lactation
- pharmacogenetics
- drugs and driving

Alerts are generated for the active ingredient as well as the excipients, like gluten in case of coeliac disease or aspartame in case of phenylketonuria.

In most cases, the drugs are not absolutely contra-indicated, but can be used under certain conditions.

Renal impairment

The practical guidelines for renal impairment contain a separate advice for the different ranges of creatinine clearance. If action is needed beneath a certain creatinine clearance, this value is recorded in a separate field. This field can be used to suppress unnecessary alerts.

For practical guidelines and transparency, see below.

Pharmacogenetics

Pharmacogenetics is a relatively young field of research.

At this moment, the G-Standaard contains alerts for pharmacokinetic polymorphisms, like different CYP-enzymes, DPD, HLA B44, HLA B5701, UGT1A1, TPMT, VKORC1 and Factor V Leiden.

Beside the practical guidelines and the datasheet, also general background information is available on both general concepts in pharmacogenetics and the polymorphisms of the enzyme.

Furthermore, for the polymorphism CYP2D6, criteria for the translation from genotype to

phenotype are available. These criteria are developed, because the translation appeared to be ambiguous in literature (and practice).

The method is published in: Swen JJ et al. Pharmacogenetics: from bench to byte. Clin Pharmacol Ther 2008;83(5):781-7. An update is published in:

For practical guidelines and transparency, see below.

Drugs and driving

In early 2008, the contra-indication 'drugs and driving' has been added to the G-Standaard. The practical guidelines include information about the legal status of driving under influence of medication. The content is based on the list of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS), supplemented with original literature.

Practical guidelines

The alerts that appear on the screen of the healthcare professional, are accompanied with practical guidelines how to deal with the alert. Furthermore, some information about the mechanism and the consequences of the interaction are included.

Transparency of evidence

All contraindications, including renal impairment and pharmacogenetics, are based on original literature. The literature and the practical guideline are assessed by a multidisciplinary expert group with day to day clinical experience. The pharmacogenetic data have an alphanumeric code, to indicate the level of evidence and the severity of the consequences of the gene-drug-interaction. The data for renal impairment have only a code for the level of evidence. The literature and (alpha)numeric code is available for the healthcare professional in a separate datasheet.

2.3 Dosage check

The following items can be checked:

- the upper limit of a dosing range (standard maximum) and the absolute maximum amount that can be given (absolute maximum)
- the lower limit of a dosing range, for example in case of antibiotics
- dose per indication
- dose per age
- dose per kilogram of body weight
- dose per m² of body surface
- dose per route of application
- the frequency (how many times a day, a week etc.)
- gender, for products only for a certain gender such as the contraceptive pill.

With this module, not all can be controlled, such as checking starting schemes. In this case the system would have to report that automatic control is not possible.

Some substances have a small therapeutic window. For these drugs, an attribute 'risk substance' is included which can be used in checking the dosage. Normally the software can generate an alert at 120-125% of the maximum dose, in case of a risk substance this happens already at 100% of the maximum dose.

2.4 Allergy

Bases on the G-Standaard, alerts for allergy for the individual drugs (active ingredients and excipients) can be generated as well as alerts for cross-reactivity. To generate an alert for cross-reactivity, the G-Standaard contains groups of drugs that are designated to cause cross-reactivity.

For the electronic health record, a standard has been developed for the logging of allergy data. With the aid of this standard, it can be recorded who has established the allergy and how, the symptoms and whether the previous prescriber judges it safe to prescribe the medication again.

2.5 Duplicate therapy

Alerts for duplicate therapy include alerts for combining drugs from the same pharmaceutical class as well as combining drugs with the same active ingredient but a different feature like a different strength or a different route of administration. These alerts are divided in 9 different classes, depending on the type of difference between the drugs.

Each class has a separate practical guideline on how to deal with the alert.

2.6 Data for labeling

The G-Standaard contains label instructions for the patient. These are instructions about for example the time of ingestion, ingestion with food or fluids like milk or grapefruitjuice, the period of usage after opening the product and storage conditions.

2.7 Special features

Some drugs need special attention of the healthcare professional. For example: drugs that have a special legal status like opioids, drugs that are involved in a monitoring program of the Dutch adverse reaction centre or a risk management programme (isotretinoin, lenalidomide), orphan drugs etc. For these kind of drugs there are separate alerts, if needed with an advice on how to deal with the alert.

2.8 Substitution

For some drugs, generic substitution can cause problems. This can be the case for drugs with a narrow therapeutic window and / or a specific kinetic profile. For these drugs, the G-Standaard contains alerts that makes healthcare professionals aware of potential problems which might rise for the client.

2.9 Age

Some drugs should not be used in children, because of the harmful effect for the child or because of ineffectiveness.

For these drugs, in the G-Standaard it is assigned until which age the drug should not be used, including a text with some background information.

Royal Dutch Pharmacist's Association (KNMP)

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