NELSON MANDELA UNIVERSITY

MEDICINES UTILISATION RESEARCH IN AFRICA GROUP
MURIA

Application of WHO ATC/ DDD methods in medicine utilisation research: A hands-on experience

Ilse Truter

2019

DRUG UTILIZATION RESEARCH UNIT
NAVORSINGSEENHEID VIR GENEESMIDDELGEBRUIK
DURU

MEDICINES UTILISATION RESEARCH IN AFRICA (MURIA)

MONDAY 8 JULY 2019

WORKSHOP
Application of WHO ATC/DDD methods in medicine utilisation research:
A hands-on experience

The application of the World Health Organization (WHO) Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) Methodology in Medicines Utilisation Research Workshop will provide participants with the basic theory of the ATC/DDD system together with practical exercises. The workshop is designed to improve understanding of the ATC/DDD Classification System, and is aimed at healthcare professionals who are involved in prescribing, formulary management, essential medicine lists, drug utilisation and related fields, and who wish to obtain a basic knowledge and skills in the practical application of this international coding language and comparative tool for drug utilisation studies. A hands-on, interactive approach will be followed and participants do not need any prior knowledge of the ATC/DDD system. The workshop presenter is a member of the WHO International Working Group for Drug Statistics Methodology.

Facilitator: Prof Ilse Truter

PROGRAMME (4 hours)

13:45 - 14:00	Introduction
14:00 - 14:15	Background
14:15 – 14:45	ATC classification
14:45 - 15:15	Defined Daily Dose (DDD)
15:15 – 15:30	ATC/DDD assignments and alterations, and combinations
15:30 - 16:00	*Tea break*
16:00 – 16:45	Applications of the ATC/DDD methodology, and ATC/DDD in drug consumption statistics
16:45 – 17:30	Practical use of the ATC/DDD methodology
17:30 - 17:45	Feedback and closure

Workshop Overview

- Introduction
- Background
- ATC classification
- Defined Daily Dose (DDD)
- ATC/DDD assignments and alterations
- Combinations
- Applications of the ATC/DDD methodology
- ATC/DDD in drug consumption statistics
- Practical use of the ATC/DDD methodology

Definitions

- ATC: Anatomical Therapeutic Chemical
- DDD: Defined Daily Dose

⇓

Classifying and quantifying drug (medicine) use

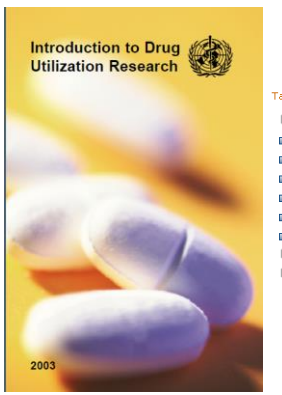
"*International language for drug utilisation research*"

To standardise studies, need …

- A **drug (medicine)** classification system, e.g.
  - Anatomical Therapeutic Chemical (ATC) classification
  - Monthly Index of Medical Specialities (MIMS)
  - British National Formulary (BNF)
  - European Pharmaceutical Market Research Association (EphMRA) and classification system (IMS Health/Quintiles)
  - Others
- A **disease (diagnosis)** classification system, e.g.
  - International Classification of Diseases, version 10 (ICD-10)
  - Others

Guideline

Available at: http://apps.who.int/medicinedocs/pdf/s4876e/s4876e.pdf



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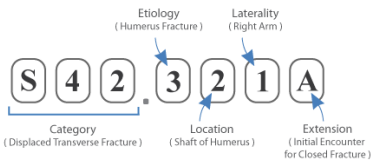
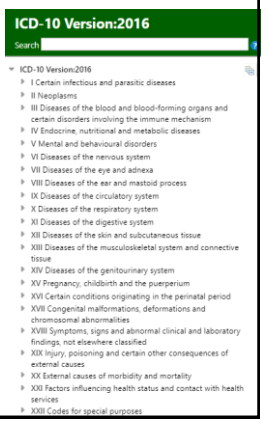
Disease Classification System

International Statistical Classification of Diseases and Related Health Problems 10th Revision

Website: https://icd.who.int/browse10/2016/en

ICD-10 Code





BACKGROUND

Many new drugs …

- **Thalidomide disaster and others**
  - Need for improved drug regulation, pharmacovigilance and monitoring drug use
  - Increased interest in drug utilisation research (DUR)
- **Why is DUR needed?**
  - Improved drug use, decision support, intervention and pharmacovigilance
  - Compare use & changes in use over time
  - Basis for assessment & guidelines to improve drug use

History of ATC/DDD[1,2]

- Developed in Norway (in collaboration with European researchers) in early 1970s
- 1976 – Nordic Council on Medicines published "*Nordic statistics on Medicines*" using the methodology
- 1982 – WHO Regional Office for Europe established the WHO Collaborating Centre for Drug Statistics Methodology
- 1996 – agreement with WHO in Geneva concerning global activity of the Centre

[1] Guidelines for ATC classification and DDD assignment 2019, 22nd Ed. 2019. Norway: WHO Collaborating Centre for Drug Statistics Methodology.
[2] Ittleskare I. 2019. Introduction and historical background. ATC/DDD Course in Cape Town, South Africa, February 2019.

"International language for drug utilisation monitoring and research"

Tool for drug utilisation monitoring and research, to:

- Present drug utilisation research
- Improve quality of drug use
- Group drugs to facilitate retrieval

WHO Collaborating Centre for Drug Statistics Methodology[1,2]

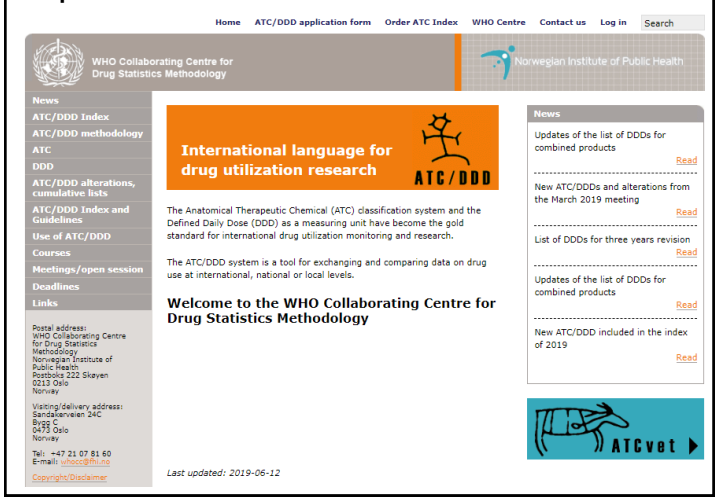
- 1982 - Established as a European WHO Centre
- 1996 - Became a global WHO Centre

- Situated in the Norwegian Institute of Public Health, Oslo
- Staff: Director, senior advisers, senior researcher & secretary
- Global expert group (WHO International Working Group for Drug Statistics Methodology) – 12 members

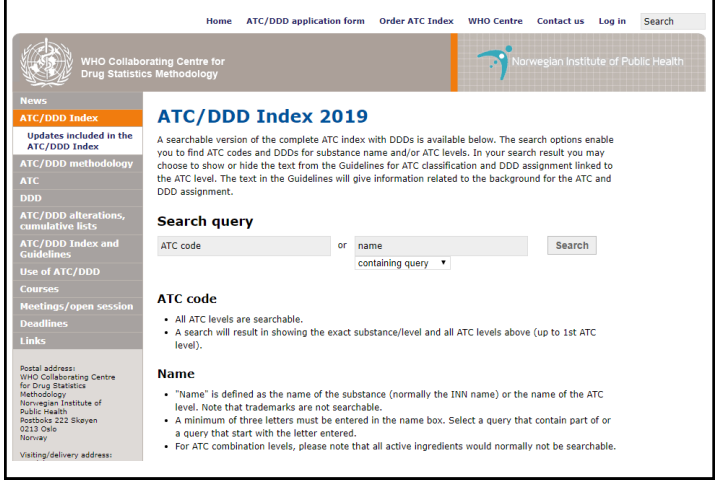
- Classify drugs according to ATC system, establish and assign DDDs, review and revise, practical application and training

[1] Guidelines for ATC classification and DDD assignment 2019, 22nd Ed. 2019. Norway: WHO Collaborating Centre for Drug Statistics Methodology.
[2] Ottleskare I. 2019. Introduction and historical background. ATC/DDD Course in Cape Town, South Africa, February 2019.

https://www.whocc.no/



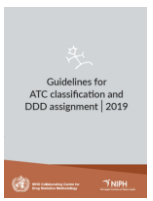
https://www.whocc.no/atc_ddd_index/

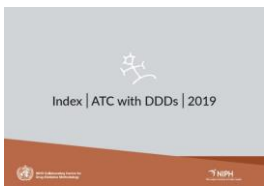


ATC/DDD Publications

- Guidelines for ATC Classification and DDD assignment
  https://www.whocc.no/filearchive/publications/2019_guidelines_web.pdf
- ATC Index with DDDs
  https://www.whocc.no/atc_ddd_index_and_guidelines/atc_ddd_index/

Annually updated, available in English and Spanish





ATC CLASSIFICATION

Why is the ATC system important?

- Obtain accurate information in epidemiological studies
- Different levels allow comparisons to be made according to purpose of study

ATC main groups (1st level)

A Alimentary tract and metabolism
B Blood and blood forming organs
C Cardiovascular system
D Dermatologicals
G Genitourinary system and sex hormones
H Systemic hormonal preparations, excl. sex hormones and insulins
J Antiinfectives for systemic use
L Antineoplastic and immunomodulating agents
M Musculo-skeletal system
N Nervous system
P Antiparasitic products, insecticides and repellents
R Respiratory system
S Sensory organs
V Various

ATC Structure

- **1st level**
  14 main anatomical or pharmacological groups (previous figure)
- **2nd level**
  Pharmacological or Therapeutic subgroup
- **3rd & 4th levels**
  Chemical, Pharmacological or Therapeutic subgroup
- **5th level**
  Chemical substance

(2nd, 3rd and 4th levels often used to identify pharmacological subgroups, when that is more appropriate than therapeutic or chemical subgroups)

Example: Metformin

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excl. insulins (3rd level, pharmacological subgroup)
A10BA	Biguanides (4th level, chemical subgroup)
A10BA02	metformin (5th level, chemical substance)

For the chemical substance: International Nonproprietary Name (INN) is preferred. If INN names are not assigned, USAN (United States Adopted Name) or BAN (British Approved Name) names are usually chosen

Principles

- Medicinal substances - classified according to main therapeutic use
- Only one ATC code for each administration form
- Several ATC codes:
  - If clearly different therapeutic uses reflected in different:
    - Routes of administration (e.g. topical, systemic)
    - Strengths
- Products containing ≥2 active ingredients = combinations (given different ATC codes from products with one active ingredient)
- WHO Collaborating Centre, Oslo establishes new entries in ATC classification on requests from users (e.g. pharmaceutical companies, regulatory agencies and researchers)

Different indications - one ATC code

Example duloxetine

- Major depressive disorder (30 mg, 60 mg)
- Stress urinary incontinence (20 mg, 40 mg)
- Diabetic neuropathic pain

Overlapping dosages for the various indications

ATC code: N06AX21 (as antidepressant)

Several ATC codes – "one indication"

M05 DRUGS FOR TREATMENT OF BONE DISEASES
M05B DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION
M05BA Bisphosphonates
M05BB Bisphosphonates, combinations
M05BC Bone morphogenetic proteins
M05BX Other drugs affecting bone structure and mineralization

Drugs used for the treatment of bone diseases, see also:
- A11CC - *Vitamin D and analogues*
- A12A - *Calcium*
- A12AX - *Calcium, combinations with vitamin D and/or other drugs*
- A12CD - *Fluoride*
- G03C/G03F - *Oestrogens/Progestogens and oestrogens in combination*
- H05BA - *Calcitonins*

Several ATC codes – different administration forms

Prednisolone

A07EA01 Intestinal antiinflammatory agents (enemas and foams)
C05AA04 Antihemorrhoidals for topical use (suppositories)
D07AA03 Dermatological preparations (creams, ointments & lotions)
H02AB06 Corticosteroids for systemic use (tablets, injections)
R01AD02 Nasal decongestants (nasal sprays/drops)
S01BA04 Ophthalmologicals (eye drops)
S02BA03 Otologicals (ear drops)

DEFINED DAILY DOSE (DDD)

Defined Daily Dose (DDD)

The assumed average maintenance dose per day for a drug used for its main indication in adults (weighing 70 kg)

- DDDs - a fixed measurement unit, independent of price, currencies, package size & strength to assess trends in drug utilisation and to perform comparisons between population groups
- Technical unit of measurement – represents an "average" daily dose for the main indication

Guidelines for ATC classification and DDD assignment 2019

Why needed?

- Measuring unit is needed
- Long-term studies of drug consumption
- Comparison of alternative therapies
- International and local comparisons

⇨ Measuring and comparing volume of drug use

Not a "correct dose" (recommended or prescribed dose), but an international compromise based on review of available documentation

Examples of DDDs

Active: Figure & unit & route of administration, e.g. "2 g O"

- **Acetylsalicylic acid (N02BA01)**
  - Oral: 3 gram
  - Parenteral: 1 gram (expressed as lysine acetylsalicylate)
- **Paracetamol (N02BE01)**
  - Oral: 3 gram
  - Parenteral: 3 gram
  - Rectal: 3 gram
- **Simvastatin (C10AA01)**
  - Oral: 30 mg

1. Main indication
2. Maintenance dose
3. Administration form

Main indication

Different indications – one ATC code

e.g. Gabapentin

- Antiepileptic – N03AX12 – DDD based on epilepsy
- Neurological pain

DDDs for antidepressants based on treatment of ***moderately severe*** depression

Determine DDD from:

Submitted documentation from applicant, textbooks & data from clinical trials

Maintenance dose

Therapeutic dose used in monotherapy normally basis for DDD (initial dose may be high or low)

Exceptions (e.g. for prophylaxis) – see Guidelines

Duration of treatment usually not taken into account, except:

Treatment > one week: DDD based on maintenance dose

Treatment < one week:

$$\text{DDD} = \frac{\text{total course dose}}{\text{Number of treatment days}}$$

Administration form

- DDD often same for various dosage forms of same drug
  - N02AX02 Tramadol 0.3 g O, P, R
- When *bioavailability* is substantially different, different DDDs will be assigned
  - N02AA01 Morphine 0.1 g O
    30 mg P
    30 mg R

DDD Principles

- Only assigned for drugs with an ATC code (not established for all drugs with an ATC code, e.g. eye drops, topical preparations)
- DDD will normally not be assigned for new substance before product is approved & marketed in at least one country
- Principle is to assign only one DDD per route of administration within an ATC code (e.g. oral formulation & parenteral)
- DDD is sometimes a dose that is rarely/never prescribed - it is an average of 2 or more commonly used doses
- Drug utilisation data presented in DDDs give a rough estimate of consumption and not an exact picture of actual use.
- DDDs for single substances are normally based on monotherapy (exceptions in Guideline)
- Substances indicated for rare disorders with individual dosing, Working Group can decide not to assign a DDD

When a new DDD is assigned for **products with one single active ingredient**, various sources are used to get an overview of actual or expected main use of a substance. The assigned DDD is based on the following principles:

- Average adult dose used for main indication as reflected by ATC code (if recommended dose refers to body weight, an adult is considered to be a person of 70 kg)
- Maintenance dose (long term therapeutic dose) is preferred when establishing DDD (initial dose may differ from maintenance dose, but this is not reflected in the DDD)
- Treatment dose is generally used, but if prophylaxis is main indication, this dose is used (e.g. antithrombotic agents in B01A)
- DDD is usually expressed according to the declared content (strength) of the product

ATC/DDD ASSIGNMENTS AND ALTERATIONS

New ATC codes and DDDs

- New ATC codes and DDDs are assigned on request (e.g. pharmaceutical companies, regulatory agencies & researchers)
- WHO Centre in Oslo
- Application form on website
- Electronic application is preferred
  - Application form
  - Basic information about the new substance
  - Proposal for an ATC code and/or DDD
  - Information on regulatory status

Inclusion in the ATC/DDD system

Included:

- New chemical entities for licensing in a range of countries
- Well-defined chemical entities used in a variety of countries, preferably with INN
- Some herbal products with dossiers including efficacy, safety and quality data
- Generally not included:
  - Complementary, homeopathic and herbal traditional products
- "Borderline" products considered on a case-by-case basis

When are new ATC codes and DDDs assigned

- **ATC codes** normally not assigned before an application for marketing authorisation (MA) is ready for submission in at least one country
  - Straightforward applications: 6-8 weeks, only approved at next WHO Working Group meeting
  - Difficult applications: Discussed at Working Group meeting, and notification 4-6 weeks later
- **DDDs** are not assigned before MA is granted in at least one country

WHO Working Group

- Two meetings annually:
  March & October
- Not only new applications, also alterations
- Also handle objections
- Strict deadlines to adhere to

Example of timeframe:

Submit new application before 15 Jan 2019, if no objections, possible inclusion in ATC Index 2020

ATC and DDD alterations

- Final alterations are implemented once annually (January)
- Webpage contains codes – temporary, final and not yet implemented
- Important to describe the version of ATC/DDD system use in research

COMBINATION PRODUCTS

Definitions

Plain products

= one active ingredient

(may contain auxiliary substances to increase the stability, duration and/or absorption of product)

Combination products

Contain two or more active ingredients

*Principle: Classify according to **main** therapeutic use or pharmacological class*

Combinations NOT belonging to the same 4th level:

Main active ingredient is identified and combination is given a separate 5th level code (50-series) in the 4th level of the main ingredient

E.g. N02BE01 Paracetamol
N02BE51 Paracetamol, combinations excl. psycholeptics
N02BE71 Paracetamol, combinations with psycholeptics (seldom)

Combinations with 2 or more active ingredients in the same 4th level:

Normally classified using the 5th level codes 30 (or 20)

E.g. N01BB02 *Lidocaine*
- N01BB04 *Prilocaine*
- N01BB20 *Combinations of lidocaine and prilocaine*

Separate ATC 3rd or 4th levels have been established for "important" combinations

DDDs for combination products

- Normally not included in ATC Index
- Principles for assignment of DDDs for combinations are given in the Guidelines
  - E.g. N06AJ06 Codeine 50 mg/paracetamol 0.5 g tablets = 3 UD (= 3 tablets)

UD = Unit Dose

Philosophy:

Combination is counted as ONE daily dose regardless of number of active ingredients in the combination

APPLICATIONS OF THE ATC/DDD METHODOLOGY

Different applications

- Recommended use
  - Drug utilisation monitoring and research
  - Pharmacoepidemiology
  - Pharmacovigilance
  - Drug lists (essential medicines lists) – e.g. SAMF, WHO Essential Drug List
- Regulatory issues, e.g. health policy
- Use in pricing and reimbursement (?)

Importance of consistency

- Stable ATC/DDD system is needed to study drug trends over time
- Reluctance to make changes to ATC codes or DDDs

ATC/DDD system by itself is not suitable for guiding decisions about pricing, reimbursement and therapeutic substitution

Practical use of ATC codes

- Facilitate retrieval of data from big data sets
- Can link use of a medicine to number of adverse drug reaction reports
- Detect drug interactions
- Signal generation in pharmacoepidemiological studies
- Determine to what extent increased costs can be attributed to increased use of a drug group

Practical use of DDDs

- Measure consumption
- Compare costs of two formulations of the same active ingredient
- Follow expenditure of a certain treatment
- DDDs:
  - Not based on equipotency data
  - Duration of treatment not considered
  - Independent of “quality” of treatment, side effects and outcomes

DDDs = International compromise

In summary

The classification of a substance in the ATC/DDD system is not:

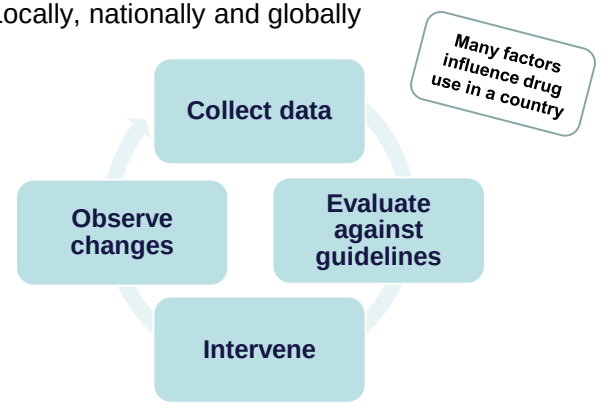
- A recommendation for use
- An implication of judgement about efficacy

It is a tool for drug utilisation monitoring and research with the aim of improving drug use

ATC/DDD IN DRUG CONSUMPTION STATISTICS

Need for data

- Need data for planning and to make improvements
- Locally, nationally and globally



Units of measurement

- **Volume**
  - Weight (mg, g)
  - Number of packages
  - Number of dosage units (e.g. tablets, capsules)
  - Number of DDDs
- **Expenditure/cost**
  - Ex factory price
  - Single Exit Price (SEP)
  - Pharmacy purchase price
  - Retail price
  - Reimbursement price
- **Other, e.g.**
  - Number of users
  - Number of prescriptions

Prescribed Daily Dose (PDD)

- The average dose prescribed according to a representative sample of prescriptions
- = Doses used in actual practice – average daily amount of a drug that is actually prescribed – and that relates to the indication for the prescribed drug
- Determined from prescription studies, medical/pharmacy records & patient interviews
- If substantial discrepancy between PDD and DDD – need to take this into account when evaluating drug consumption figures

Implementation of ATC/DDD

- Link each medicine package to appropriate ATC code and DDD
- Check that ATC groups from different countries are comparable/the same
  - Unofficial ATC codes
  - Classification of combination products
  - Products with different ATC codes for different formulations/strengths

Recommended variables for national registries (and studies)

- Unique identifier (registration number)
- Medicinal product name (brand name/trademark)
- Pharmaceutical form
- Strength
- Pack size
- ATC code
- Active ingredient(s)
- DDD
- Route of administration
- Number of DDDs in the pack

DDD indicators

- Expressed in units to control for population size differences – measure of exposure / therapeutic intensity in a defined population (allowing comparisons across various time periods & population groups)

- Normally: DDDs/1000 inhabitants/day
- Also:
  - DDDs/inhabitant/year
  - DDDs/day
  - DDDs/patient per year
  - DDDs/100 bed-days (hospital)

Drug Utilisation 90% (DU90%)

- Reflects number of drugs that account for 90% of drug prescriptions & adherence to local/national prescription guidelines
- Innovative way to assess prescribing patterns
- Assumption: Low number of drugs prescribed is associated with more rational prescribing practices
- To explore drug prescription in a rapid, effective & inexpensive way

Similarly, can calculate Drug Cost 90% (DC90%)

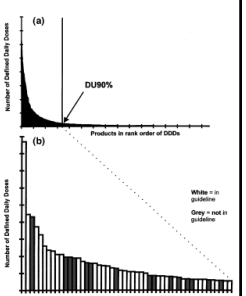


Fig. 1 a Number of drugs ranked by volume of defined daily doses (DDD). The arrow indicates the number of drugs accounting for 90% of the DDDs (DU90%; the area under the curve) b The DU90% segment enlarged, indicating drugs listed in a guideline (white) and drugs not listed (black). Index of adherence is calculated as the percentage of the number of DDDs in white/green of the total number of DDDs in this segment

Are published data comparable?

Essential to know:

Which version of ATC codes and DDDs are used?

Important to be aware of alterations

Example:

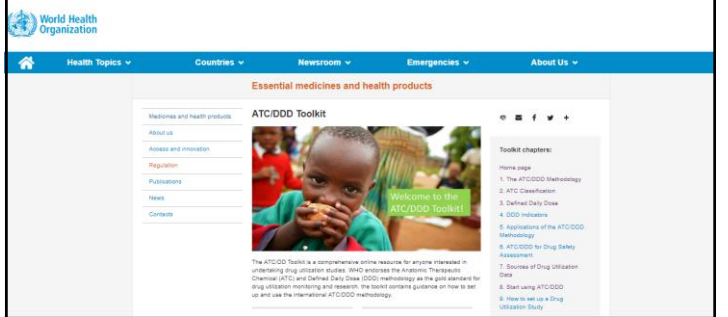
Statins – C1-AA (changed twice, latest 2009)

(this influences statistics and needs to be recognised in reports)

NB to properly reference the ATC/DDD version that was used in publications

PRACTICAL USE OF THE ATC/DDD METHODOLOGY

https://www.who.int/medicines/regulation/medicines-safety/toolkit/en/



In summary

- ATC/DDD system is “the gold standard” for international drug utilisation research
- ATC/DDD is a tool for exchanging and comparing data on drug use at local, national or international levels

Exercises

References

- ATC Index with DDDs 2019. 2018. Oslo: WHO Collaborating Centre for Drug Statistics Methodology.
- ATC/DDD Toolkit. 2019. Available at: https://www.who.int/medicines/regulation/medicines-safety/toolkit/en/ (date accessed: 26 June 2019).
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Thank you!

Guidelines for ATC classification and DDD assignment | 2019

WHO Collaborating Centre for Drug Statistics Methodology

NIPH
Norwegian Institute of Public Health

C10 LIPID MODIFYING AGENTS

The DDDs are based on the treatment of hypercholesterolemia.

C10A LIPID MODIFYING AGENTS, PLAIN

Pantethine, which is also used in the treatment of hyperlipidemi, is classified as a vitamin in A11HA.

C10AA HMG CoA reductase inhibitors

This group comprises agents which act as competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase). Atorvastatin in combination with amlodipine is classified in C10BX03.

C10AB Fibrates

Clofibrate and analogues are classified here.

The DDD for fenofibrate is based on the micronised formulation.

C10AC Bile acid sequestrants

This group comprises substances (such as colestyramine and colestipol) which reduces the cholesterol level by increasing the excretion of bile acid.

C10AD Nicotinic acid and derivatives

This group comprises high strength preparations (e.g. nicotinic acid tab 500 mg) used as cholesterol reducers. Nicotinic acid or derivatives in low strength preparations (e.g. nicotinic acid tab 50 mg) are classified in C04A - *Peripheral vasodilators*.

Combinations of nicotinic acid and laropiprant are classified in C10AD52.

C10AX Other lipid modifying agents

This group comprises all cholesterol and triglyceride reducers, which cannot be classified in the preceding groups.

Sulodexide is classified in B01AB.

The DDD for evolocumab is based on dosing every second week.

C10B LIPID MODIFYING AGENTS, COMBINATIONS

Fixed combinations of blood glucose-lowering drugs and lipid modifying agents are classified in A10B.

For fixed combinations in C10B the DDD is based on dosing frequency only. This implies that 1 UD (1 tablet) is the DDD for all products given once daily and the DDD for products given twice daily and three times daily is 2 UD (2 tablets) and 3 UD (3 tablets) respectively.

C10BA HMG CoA reductase inhibitors in combination with other lipid modifying agents

C10BX HMG CoA reductase inhibitors, other combinations

Combinations with e.g. ACE inhibitors, angiotensin II antagonists, calcium channel blockers or diuretics are classified in C10BX.

https://www.whocc.no/atc_ddd_index/?code=C10A&showdescription=no

WHO Collaborating Centre for Drug Statistics Methodology

Norwegian Institute of Public Health

News
ATC/DDD Index
Updates included in the ATC/DDD Index
ATC/DDD methodology
ATC
DDD
ATC/DDD alterations, cumulative lists
ATC/DDD Index and Guidelines
Use of ATC/DDD
Courses
Meetings/open session
Deadlines
Links

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Bygg C
0473 Oslo
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C CARDIOVASCULAR SYSTEM
C10 LIPID MODIFYING AGENTS
C10A LIPID MODIFYING AGENTS, PLAIN
C10AA HMG CoA reductase inhibitors
C10AB Fibrates
C10AC Bile acid sequestrants
C10AD Nicotinic acid and derivatives
C10AX Other lipid modifying agents

Last updated: 2018-12-13