EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

SmPC and older people

SmPC training presentation

Note: for full information refer to the European Commission's Guideline on summary of product characteristics (SmPC)

SmPC Advisory Group

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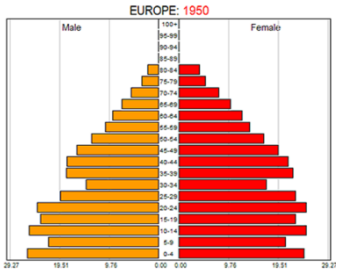
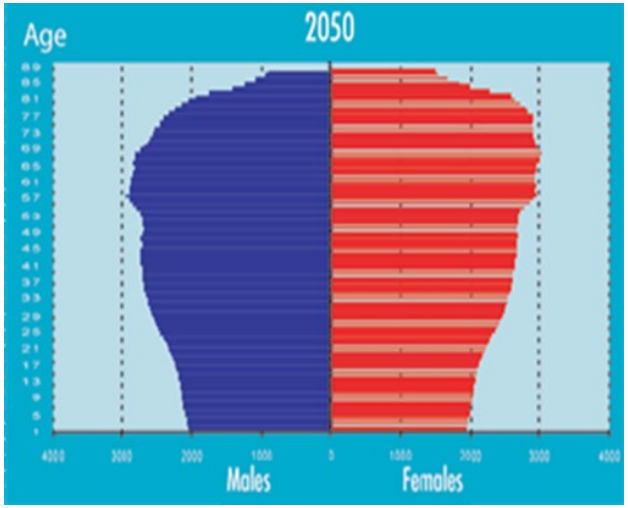
Information on the use of medicines in older people is a PRIORITY

- EU Ageing population
- Older people are often the main users of medicines
- Public demand for better information
- Support informed prescription and use
- Safe and effective use in older people





Section index

Older people

- A heterogeneous group of individuals from healthy to seriously ill
- Older people's bodies take up and eliminate medicines from the body differently to younger people
- Older people may be more sensitive to pharmacodynamic effects
- Older people often have more than one disease at a time
- Older people have been underrepresented in clinical trials
- Consistency of the treatment effect and safety profile in different patients should be assessed in various age groups (for example <65, 65-74, 75-84 and > 85)

How can the SmPC contribute to safe and effective use of medicine in older people?

- By providing clear and concise information throughout the SmPC in accordance with the SmPC guideline
- By communicating known factors which may influence benefits or risks of the medicine in older people
  - Not only in relation to age physiological changes
  - But also regarding concomitant diseases and drug interactions
- By informing on lack of data or limitation of available data in case of uncertainties on the use in older people

Do not forget the package leaflet

- A clear SmPC is key for preparing clear package leaflet
  - The package leaflet reflect information deriving from the evaluation dossier as this is presented in the SmPC
  - Scientific information included in the SmPC has to be translated into meaningful information for the user in the package leaflet
- Older people are less amenable to "modern" methods of getting information
- Design and layout of the package leaflet should be suitable to the end user, e.g. consider age-related visual impairment

General principles

- Each section of the SmPC should first deal with those issues that apply to the core population for whom the medicine is indicated followed, when necessary, by specific information for any relevant special population
  - For some medicine or indication, older people will represent the core population
  - In other cases, it should be considered whether there is any specific information for older people or patients with co-morbidity to be communicated
  - Use of sub-heading will facilitate identification of information on subpopulation
- Stating only "Use with caution" or "There is limited data" is not sufficiently informative; information should try to support clinical practice

Therapeutic indication

- Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug (ICH E7)
- The therapeutic indication should define the target population especially when restrictions to the patient populations apply
- Lack of data alone should not lead to a contraindication
- Posology recommendation must be available for the entire target population of the therapeutic indication

4.2 Posology and method of administration

It should be made clear whether or not any dosage adjustment is necessary in any subsets of the older population, with cross-reference to other sections providing information in this population

Examples

When supportive data are available, information on alternative method(s) to facilitate administration or acceptability should be given as explicitly as possible (e.g. possibility of crushing tablet, cutting tablet…)

Examples

Examples of posology information on older population in section 4.2:

Older patients may be sensitive to the effects of hypnotics; therefore, 5 mg is the recommended dose of X.

Dosing recommendations for older patients with normal renal function (80 ml/min) are the same as for adults with normal renal function. However, because older patients may have diminished renal function, dose adjustments may be required according to their renal function status (see Renal impairment below).

There are only limited data on the safety and efficacy of X in patients aged 65 years and above. A reduction in the initial and maintenance dose of X is recommended in elderly patients. The total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended (see sections 4.4 and 5.2).

Examples of information on alternative method of administration in section 4.2:

For patients who are unable to swallow tablets, X is available as an oral solution. Alternatively, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

Patients should not chew, suck or crush the tablet because of a potential for oropharyngeal ulceration.

4.4 Special warnings and precautions for use

Special patient groups that are at increased risk or are the only groups at risk of experiencing product or product class-related adverse reactions (usually serious or common), e.g. elderly, children, patients with renal or hepatic impairment (including the degree of impairment, e.g. mild, moderate or severe), patients having an anaesthesic or patients with cardiac failure

Examples

Examples of class warnings

Examples of warnings and precautions for use in the older population

X may induce orthostatic hypotension and syncope, especially early in treatment. Elderly patients are particularly at risk for experiencing orthostatic hypotension. In clinical trials, cases of syncope were occasionally reported during treatment with X. X should be used with caution in elderly patients and in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension.

Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In an exploratory analysis, increasing age, especially aged 65 years and older, appeared to be associated with increased rates of neurological adverse events.

X should be used with caution in elderly patients, who may be more sensitive to the effects of centrally acting anticholinergics and exhibit differences in pharmacokinetics.

Examples of class warnings in the older population

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Increased Mortality in Elderly people with Dementia
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.
{Invented name} is not licensed for the treatment of dementia-related behavioural disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

If there are patient groups in which the impact of an interaction is more severe, or the magnitude of an interaction is expected to be larger e.g., patients with decreased renal function (in case the parallel pathway is renal excretion), paediatric patients, elderly, etc., this information should be given in section 4.5

Examples

Examples of drug interaction information in the older population

Non-steroidal anti-inflammatory drugs: when angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should be then be reinforced.

4.8 Undesirable effects

This section may include information on any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, patients with hepatic impairment, patients with other diseases or a specific genotype

Examples

Examples 4.8

The incidence of orthostatic hypotension in elderly subjects was 4.1 % compared to 0.3 % in the combined phase 2/3 trial population.

Elderly patients (≥ 65 years):
Elderly patients (≥ 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving X as part of a combination immunosuppressive regimen may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

Elderly population
Based on the results of a phase 3 study in renal cell carcinoma, elderly patients (> 65 years of age) may be more likely to experience certain adverse reactions, including oedema, diarrhoea, and pneumonia. Based on the results of a phase 3 study in mantle cell lymphoma, elderly patients (> 65 years of age) may be more likely to experience certain adverse reactions, including pleural effusion, anxiety, depression, insomnia, dyspnoea, leukopaenia, lymphopaenia, myalgia, arthralgia, taste loss, dizziness, upper respiratory infection, mucositis, and rhinitis.

Class effects - Section 4.8 for all SSRIs and TCAs
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

4.9 Overdose

Information specifically observed in special populations such as elderly, patients with renal impairment, patients with hepatic impairment, other concomitant diseases, etc.

Example: Guideline on core SmPC for human normal immunoglobulin for intravenous administration

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment.

5. Pharmacological properties

Examples

It may be appropriate to provide limited information, relevant to the prescriber, such as the main results regarding pre-specified end points or clinical outcomes in the major trials, and giving the **main characteristics of the patient population**

When clinically relevant information from **subgroup** analyses is presented, it should be identified as such in a **balanced** manner reflecting the limited robustness of both positive and negative secondary observations

Regarding pharmacokinetic properties, variations with respect to factors such as **age**, weight, gender, smoking status, polymorphic metabolism and concomitant pathological situations such as renal failure, hepatic disease, including degree of impairment should be presented in section 5.2. If the influence on pharmacokinetics is considered to be clinically relevant, it should be described in quantitative terms (cross-reference to section 4.2 when applicable)

Examples

Examples 5.1

A total of 675 patients were randomized to X (n=337) or Y (n=338). Most patients were male (56%) and Caucasian (99%), the median age was 54 years (24% were ≥ 65 years), all patients had Eastern Cooperative Oncology Group Performance Status performance status of 0 or 1, and the majority of patients had stage M1c disease (65%).

The effect of X once a day in elderly depressed patients (≥65 years) was specifically examined in a study that showed a statistically significative difference in the reduction of the HAMD17 score for X-treated patients compared to placebo. Tolerability of X once daily in elderly patients was comparable to that seen in the younger adults. However, data on elderly patients exposed to the maximum dose (120mg per day) are limited and thus, caution is recommended when treating this population.

For the primary safety endpoint of major bleeding there was an interaction of treatment effect and age. The relative risk of bleeding with X compared to Y increased with age. Relative risk was highest in patients ≥ 75 years.

Example 5.2

Elderly

Long-term controlled data in elderly are limited, but suggest no marked changes in X exposure with increased age up to about 75 years old. In a pharmacokinetic study in patients with type 2 diabetes, administration of X (10 µg) resulted in a mean increase of X AUC by 36 % in 15 elderly subjects aged 75 to 85 years compared to 15 subjects aged 45 to 65 years likely related to reduced renal function in the older age group (see 4.2).

More information on medicines and older people

- ICH Topic E 7 - Studies in Support of Special Populations: Geriatrics (CPMP/ICH/379/95) and Questions and answers on the guideline
- EMA web page "Medicines for older people"
- EMA geriatric medicines strategy
- CHMP Geriatric Experts Group mandate and composition

Thank you for consulting this training presentation

SmPC Advisoy group

Please note the presentation includes examples that may have been modified to best illustrate the related principle.