



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

## EMA Geriatric Medicines Strategy

### Report analysis on Product Information

#### Introduction

One of the pillars of the European Medicines Agency (EMA) vision for geriatric medicines is to improve the availability of information on the use of medicines for older people, thereby helping informed prescription.

As a concrete action, it was proposed to ensure accurate reflection in the product information of any geriatric findings, or lack of data in the geriatric population.

#### Objectives

This brief report summarises the results of the first year of the Geriatric Strategy implementation with respect to Product Information for newly authorised medicinal products, and analyses whether data on the geriatric population is accurately presented and critically discussed in the final CHMP Assessment Report and Product Information (Summary of Product Characteristics and Patient Information Leaflet).

The EMA Geriatric Medicines Strategy foresees that for products under evaluation, as part of the Peer review comments, the Agency will send any comments considered relevant concerning geriatric aspects of the List of Questions to the CHMP for consideration prior to the adoption of the List.

This analysis had the main objective to quantify the comments included and rejected in the final D120 LoQ.

An additional, qualitative objective was the review of the availability of information regarding the use of the new drug in the older population shown in the EPARs, SmPCs and PILs, with a view to provide examples on the impact of the strategy in improving this information. To this end, we conducted a comparison of the information regarding the older population in the final PI with the PI initially proposed, and reviewed the measures included in the Risk Management Plan. Examples are reported to highlight different areas where action has been taken.



## Methods

This analysis covers the period from February 2011 to May 2013.

All products peer reviewed were considered as relevant to the older population. The only products excluded from the exercise were preponderantly paediatric products and generics (where the product information has to mirror the originator, therefore no action could be taken).

Eligible products were evaluated at Day 80 of the procedure for:

- compliance with ICH E7 requirements in terms of pharmacokinetics, efficacy, safety and requests for specific drug-drug interaction studies.
- presence of the tables foreseen in the day 80 CHMP Assessment Report templates to summarise efficacy and safety data in the older population.

Comments were sent during the peer review for consideration of inclusion in the day 120 List of Questions when products did not comply with ICH E7 requirements, if geriatric data appeared missing, required a separate analysis, or were not expressed clearly.

Products which had received a CHMP opinion at the time of analysis (May 2013) were included in this analysis.

## Results

A total of 81 products were peer reviewed for geriatric aspects from February 2011 (inception of the EMA geriatric Medicines Strategy) to May 2013 (cut-off date).

Of the products analysed, 43 products reached the end of the procedure during the study period. 36 products had a positive opinion, 5 products had a negative opinion and 3 products were withdrawn.

Three-quarters (75% n=61) of the products received comments for consideration in the day 120 LoQ.

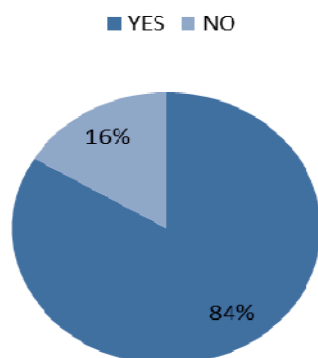
For the remaining 25% of the products, geriatric aspects appeared sufficiently covered in accordance with ICH E7, hence comments were not sent.

Number of products analysed	
Total Products	81
End of Procedure by May 2013	44
Positive opinion	36
Negative opinion	5
Withdrawn	3

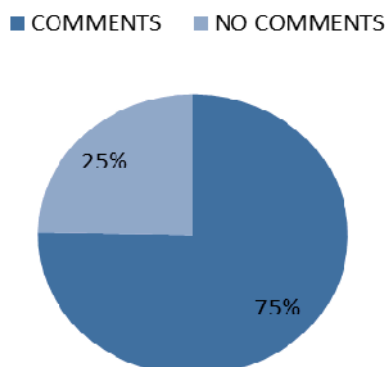
These comments were included in the Day 120 List of Questions in 84% (n=51) of the cases.

Concerning the impact this has on the approval documents, and the clarity of information and guidance provided therein, we have conducted an analysis on a sample of products, similar to what was done in 2006 ([Adequacy of the guidance on the elderly regarding medicinal products for human use](#)), to give examples of the extent of the changes in the Product Information and the impact on post authorisation measures.

## Comments Included



## Products Analysed



## PRODUCT INFORMATION EXAMPLES

### 1. [BETMIGA](#) – Cardiovascular Safety in the elderly / RMP measures

#### Indication:

Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

#### CHMP conclusions

The RMP requires the conduct of a post-authorisation safety study to further explore the CV safety particularly in the elderly. The SmPC contained relevant information regarding the observations related to cardiovascular safety.

### 2. [XALKORI](#) – Lack of safety data reflected in SmPC and post authorisation measures

#### Indication:

Treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

#### CHMP Opinion:

Of the 125 patients in study 1001, 18 (14%) were 65 years or older. Of the 261 patients in study 1005, 30 (12%) were 65 years or older. No patients in Studies 1001 or 1005 were 85 years or older. Clinical studies did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

The MAH provided the requested analysis of safety data by age groups, sex and race. Overall, 308 patients were <65 year old and 48 ≥ 65 year-old. The rate of AEs is variable but the number of patients in two groups is rather low to reveal specific drug related safety issues in any of these age groups, especially elderly patients. Therefore, the CHMP

requested a post-authorisation study as a multi-national post-approval database surveillance study including elderly patients is planned

The PK/PD of the drug has not been adequately evaluated in patients over 65 years of age and this information has been adequately reflected in sections 4.2, 4.4 and 5.1 of the SmPC. The MAH will complete an updated popPK analysis to definitively assess the effect of age on crizotinib PK using pooled data from clinical trials with the final report to be submitted on Q1 2013.

3. **ADASUVE – Lack of data in older people- SmPC wording and post authorisation measures.**

**Indication:**

Rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Patients should receive regular treatment immediately after control of acute agitation symptoms.

*CHMP Opinion:*

Identified as important missing information no data for use in elderly (>65 years of age) patients due to the design of the submitted clinical studies.

There is a lack of data regarding elderly patients due to the design of the submitted clinical studies. Appropriate warnings are reflected in the SmPC.

- Section 4.2 : *"Elderly: The safety and efficacy of ADASUVE in patients older than 65 years of age have not been established. No data are available."*
- Section 4.4: *"Elderly patients with dementia-related psychosis: ADASUVE has not been studied in elderly patients, including those with dementia-related psychosis. Clinical studies with both atypical and conventional antipsychotic medicinal products have demonstrated that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. ADASUVE is not indicated for the treatment of patients with dementia-related psychosis."*

Further data are intended to be collected via a post authorisation safety study and a drug utilisation study to characterise the safety profile of Adasuve in the broader agitated population than the one included in the clinical studies and the usage of Adasuve in the approved indication in the EU. These studies are part of the risk management plan.

4. **TRESIBA – Assessment according to the requirements of ICH E7**

**Indication:**

Treatment of diabetes mellitus in adults.

*CHMP Opinion:*

In the controlled therapeutic exploratory and confirmatory trials, 1303 (20.4%) subjects > 65 years were exposed to IDeg or IDegAsp including 153 subjects  $\geq$  75 years. This is in accordance with the ICH E7 guideline. Exposure to IDeg + IDeg/Asp in the subgroup of subjects with T1DM >75 years was low (n=13, PYE = 9) and may not have been sufficient to adequately address the safety of the product in subjects with T1DM. Thus, "use in subject >75 years with T1DM" has been addressed as Missing Information in the RMP. The SmPC recommends intensified glucose monitoring in the elderly. This is considered sufficient.

5. **CONSTELLA** –Significance of ADRs in older population, SmPC wording, encouraged increased monitoring and reporting of ADRs in elderly.

**Indication:**

Symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

**CHMP Opinion:**

Only 5% of the study participants were above 65 years of age. The frequency of diarrhoea is highest among the elderly population. This being a more vulnerable population, the concurrence of diarrhoea and its consequences (hypokalaemia, low bicarbonate, dehydration, dizziness, and orthostatic hypotension) might be more frequent or more severe. Appropriate statements have been included into the SmPC, stressing that prescribers should afford special attention to older patients and review the medicine's benefits and risks carefully before and during treatment in this age group. To further elucidate the safety profile of the medicine in this population, the MAH will perform a post-authorisation safety study that specifically includes elderly patients.

The Product Information reads as follows:

- SmPC
  - Section 4.4 (Special Warnings and Precautions for Use): "*Patients should be aware of the possible occurrence of diarrhoea during treatment. They should be instructed to inform their physician if severe or prolonged diarrhoea occurs (see section 4.8). Should prolonged (e.g. more than 1 week) or severe diarrhoea occur, medical advice should be sought and temporary discontinuation of linaclotide until diarrhoea episode is resolved may be considered. Additional caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g. elderly, patients with CV diseases, diabetes, hypertension), and electrolyte control should be considered.*"  
  
*"There are limited data in elderly patients (see section 5.1). Because of the higher risk of diarrhoea, special attention should be given to these patients and the treatment benefit-risk ratio should be carefully assessed'.*
  - Section 4.8: "*Elderly (>65 years), hypertensive and diabetic patients reported diarrhoea more frequently as compared to the overall IBS-C population included in the clinical trials*".
- Patient Information Leaflet:
  - Warnings and Precautions: "*Take special care if you are older than 65 years, as there is a higher risk you experience diarrhoea.*"

6. **FYCOMPA** – Risk of falls: labelling and post authorisation monitoring

**Indication:**

Treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

**CHMP Opinion:**

No definite conclusion could be drawn on the safety profile in patients  $\geq 65$  years due to the very low number of elderly included in the phase III studies (28/1480, 1.9%).

As dizziness, fatigue, irritability and fall, which represent some of the most frequently reported TEAEs of the phase III studies, the CHMP requested the following:

- The MAH will carry out a post-marketing observational safety study on balance disorder, ataxia, and falls (particularly in the elderly) and use in the elderly with epilepsy, with particular monitoring of dizziness, balance disorders and falls.
- SmPC section 4.2: Clinical studies of perampanel in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Analysis of safety information in 905 perampanel-treated elderly subjects (in double-blind studies conducted in non-epilepsy indications) revealed no age-related differences in the safety profile. In combination with the lack of age-related difference in perampanel exposure, the results indicate that dose-adjustment in the elderly is not required. Perampanel should be used with caution in elderly taking into account the drug interaction potential in polymedicated patients (See Section 4.4)
- SmPC Section 4.4: *"There appears to be an increased risk of falls, particularly in the elderly; the underlying reason is unclear"*.
- This is also communicated in the PIL

## Conclusions

From the high acceptance rate of the comments sent at the peer review stage, it would appear that the specific review of the geriatric aspects of an application has added value in helping clarify the amount and type of data present in the dossier with regards to safety and efficacy aspects the older population, and assists in focusing the review on these points.

This increased focus should help the reflection of the assessment conclusion in the product information and the EPAR. We have found several examples of detailed, relevant information in specific areas, particularly with respect to safety. The measures foreseen in the Pharmacovigilance legislation that entered into force in 2012 are increasingly applied to geriatric aspects, and are reflected more transparently in the EPAR. At the end of 2012 a specific training for assessors on geriatric information in the SmPC and PIL was conducted.

We expect that in the future the situation will continue to improve and plan to conduct a more detailed review once a larger sample of product has been granted a Marketing Authorisation.