Executive Summary on Service Description 2

for service contract

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EXECUTIVE SUMMARY

BACKGROUND AND PREVIOUS STUDY

A signal concerning calcification of mitral, tricuspid, as well as pulmonary valves in association with exposure to four bisphosphonates (alendronate, ibandronate, pamidronate and zoledronate) was initially identified from spontaneous reports in the post-authorisation analysis of EudraVigilance. A signal strengthening study was previously conducted by EU-ADR Alliance using data from four European electronic healthcare record (EHR) databases. In this signal strengthening study age- and sex-adjusted incidence rate ratios of overall cardiac valve disorders and valve regurgitation during bisphosphonate use (vs. non-use) were generated. A small but statistically significant increased risk of overall (nonrheumatic) cardiac valve disorders was found during use of clodronate, etidronate, risedronate, alendronate, etidronate/calcium, risedronate/calcium, and alendronate/colecalciferol. The increased risk persisted when a carry-over period of 180 days was imposed. However, upon application of another method that better addressed confounding, i.e. case control, an increased risk, although no longer statistically significant, was observed only for alendronate.

CURRENT STUDY

Design and Methodology

In this formal validation study, which employed a case control design nested in a cohort of new users of bisphosphonates, the association of cardiac valve disorders with use of bisphosphonates was evaluated more in depth. This study used data from the databases previously employed in the signal strengthening study as well as additional data from two EHR databases – the Dutch general practitioner (GP) database IPCI (Integrated Primary Care Information) and the English GP database THIN (The Health Improvement Network). This signal validation study provided: 1) more power to investigate the association of interest; 2) better control of confounding factors through design and adjustments; and 3) validation for some of the outcomes in some databases. With this dedicated data set the heterogeneity in bisphosphonates exposure across different countries, as well as the effect of duration of use, were also explored. This larger data set also allowed the investigation of the specific outcome cardiac valve calcification in three of the databases, where the event is captured either using free-text search (HSD and IPCI) and manual validation, or using a specific disease code (THIN). Several sensitivity analyses were performed such as comparisons within a cohort of users of drugs used in the treatment of osteoporosis, the main indication of use for bisphosphonates.

Results

Class effects

In this multi-database signal validation study a very small but statistically significant association was found between long-term exposure to bisphosphonates as a class and the risk of cardiac valve disorders.

Overall, the risk of cardiac valve disorders was 18% higher in current users of any bisphosphonate as compared to distant past users (more than one year of no bisphosphonate treatment). The risk of cardiac valve regurgitation specifically was 14% higher, while no increased risk of valve calcification was found with current use of bisphosphonates as a class. These findings were based on both pooled analyses and meta-analyses of single database risk estimates. There was no significant heterogeneity (p=0.13) in the overall results across the six different databases. Sensitivity analysis showed that there was no increased risk of cardiac valve disorders for current use of bisphosphonates as compared to current use of other anti-osteoporosis drugs.

Effects of individual compounds

The bisphosphonates that were consistently associated (i.e., in both pooled analyses and meta-analyses) with a small increased risk of both valve disorders in general and valve regurgitation in particular include **alendronate and risedronate**. The increased risk associated with these drugs (current vs. distant past use) was observed not only among new bisphosphonate users, but also among both users of bisphosphonates and users of any other drug for osteoporosis (extended cohort). In this sensitivity analysis within the extended cohort (but not in the main analysis), only **alendronate** was found to be associated with an increased risk of valve calcification (70-71% increased risk, based on both pooled analysis and meta-analysis of single database risk estimates).

Subanalyses

No increased risk was observed with increasing duration of bisphosphonate use (>6 months) for the overall analysis of cardiac valve disorders, but for valve calcification in particular a longer duration of use was associated with a 57% decreased risk (compared to a shorter duration, i.e., <6 months). Switching from a bisphosphonate to a non-bisphosphonate drug for osteoporosis (and vice versa) had no significant effect on the risk of valve disorders. While current use of any bisphosphonate was associated with an increased risk of valve disorders in those 65 years and older as well as in those <65 years, the risk was significant only in the younger age group particularly for **alendronate** and for **risedronate.** Current use of any bisphosphonate was associated with an increased risk of cardiac valve disorders in both males and females, but the risk of most individual bisphosphonates was statistically significant only in females.

CONCLUSIONS

In conclusion, this study confirms that current use of some bisphosphonates is associated with a small but statistically significant increase in the risk of cardiac valve disorders and in particular valve regurgitation. More specifically, a statistically significant increase was observed consistently for **alendronate** and **risedronate. Alendronate** was associated with a significant increase in the risk of valve calcification only when evaluated together with all other drugs used in the treatment of osteoporosis.