Annex

Scientific conclusions and grounds for refusal of the variation(s) presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation

This variation concerns an application for extension of the approved indications for Javlor. The MAH applied for the indication of Javlor "in combination with capecitabine for the treatment of adult patients with locally advanced or metastatic breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant."

- Efficacy issues

The proposed new indication is supported by a single pivotal study VFL 305. The effect on PFS, the primary endpoint, is modest (HR: 0.84, 95% CI: 0.71-0.99, P = 0.046) and there is no significant effect on overall survival (HR: 0.97, 95% CI: 0.83-1.14, P = 0.6976) or other important secondary endpoint e.g. response rate; 22.9% vs. 17.9%, P = 0.1030.. The claimed magnitude of effect on the primary endpoint PFS is small and supported by only positive trends in other important secondary endpoints. The results from study VFL 305 are not considered to be statistically compelling for the purpose of accepting this new indication.

Additional analyses were provided to support the effects in the combination arm, time to retreatment (TTRT) and analysis of a clinically meaningful impact on quality of life (QoL). A continuous improvement in the global health status score was apparently observed for the VFL+CAPE arm. In general, open-label clinical trials, where patients and investigators are aware of assigned therapy are rarely adequate to support specific quality of life claims. The improvement in scores is difficult to understand when one considers the consistently higher burden of adverse events in the VFL+CAPE arm. The Applicant considers that the magnitude of effect observed for the primary endpoint is comparable to the differences reported and considered as clinically meaningful with other drugs or combinations which have been approved by the EMA. The CHMP considered that there are limitations in such comparisons where studies may be dissimilar with respect to numerous important factors and has attempted to determine the prognosis of the patient populations enrolled for the 'approved therapies'. Although the MAH amended the proposed wording of the indication to better reflect the population in Study VFL 305, the CHMP considers that no firm conclusions can be drawn from this comparison and the benefit risk balance is based on the assessment of the favourable and unfavourable effects and the uncertainties. Thus, the comparison to other indications in other ABC settings has not demonstrated a positive benefit risk for vinflunine in combination with capecitabine.

- Safety issues

Patient exposure is considered to be sufficient for determining safety for the claimed indication, combining two known active medicinal products. 383 patients in the VFL+CAPE arm and 383 in CAPE arm received at least one dose of the study treatment (any of the study drugs in the combination arm). The median number of cycles per treated patient was 6.0 in the VFL+CAPE arm and 5.0 in the CAPE arm.

In terms of the incidence of adverse events, more VFL+CAPE patients experienced an adverse event, a drug-related adverse event, a serious adverse event, a serious adverse event reported as drug-related and an adverse event leading to discontinuation. As expected, the toxicity profile

is more favourable in the CAPE arm. In general, treatment emergent adverse events (regardless of relationship) were significantly more commonly experienced in the VLF+CAPE arm compared to the CAPE only arm. In particularly blood and lymphatic system disorders (any grade, 24.5% vs 12.8%), gastrointestinal events (66.8% vs. 57.4%), general disorders and administration site conditions (63.7% vs. 43.3%), musculoskeletal and connective tissue disorders (39.2% vs. 26.4%) and nervous system disorders (33.4% vs. 22.7%). As expected, related treatment emergent adverse events were significantly more commonly experienced in the VLF+CAPE arm compared to the CAPE only arm. In particularly blood and lymphatic system disorders (any grade, 22.2% vs 12.0%), gastrointestinal events (62.7% vs. 46.5%), general disorders and administration site conditions (47.5% vs. 22.7%), musculoskeletal and connective tissue disorders (19.6% vs. 3.9%), nervous system disorders (17.5% vs. 8.1%) and vascular disorders (5% vs. 1.8%). Drug-related treatment emergent AEs of special interest were significantly more commonly experienced in the VLF+CAPE arm compared to the CAPE only arm. In particular, neutropenia, constipation, abdominal pain, nausea, vomiting, stomatitis or mucositis, local injection / infusion site reactions, peripheral sensory neuropathy, asthenia/Fatigue and myalgia.

More drug-related SAE were experienced in the VFL+CAPE arm compared to the CAPE arm, in particular gastrointestinal disorders (8.1% vs. 1.8%) and blood and lymphatic system disorders (3.7 vs. 1.6). The most frequent SAEs in patients treated with VFL+CAPE were constipation (2.1% of patients) and febrile neutropenia (1.8%). At the cut-off date of 20th December 2011 (date for primary analysis), 232 patients in VFL+CAPE arm and 235 CAPE arm were dead. For deaths within 30 days of the last study drug dose, the majority of deaths were due to disease progression, 5.5% of patients treated with VFL+CAPE and 5.7% of the CAPE arm. Two deaths (0.5%) in the VFL+CAPE arm were considered secondary to a drug-related AE and one (0.3%) in the CAPE arm.

Patient's decision was a more common reason for discontinuation in the VFL+CAPE arm (11.2%) versus the CAPE arm (4.9%).

Overall, the tolerability of the combination therapy can be questioned. More VFL+CAPE patients compared to the CAPE only arm patients experienced an adverse event, a drug-related adverse event, a serious adverse event, a serious adverse event reported as drug-related and an adverse event leading to discontinuation.

In conclusion, the benefit risk balance for Javlor in the claimed new indication is considered to be negative as the additional toxicity of the combination treatment does not outweigh the observed modest improvement in PFS.

Grounds for refusal of the variation(s)

Whereas

The efficacy of vinflunine in combination with capecitabine for the treatment of adult patients with locally advanced or metastatic breast cancer not amenable to curative surgery or radiotherapy, who are capecitabine and vinca alkaloid naïve, and were previously treated with or resistant to an anthracycline and who are taxane resistant.

- has not been demonstrated due to a modest improvement in PFS being observed.

- Patient exposure is considered to be sufficient and shows an additional toxicity profile burden of the combination of vinflunine with capecitabine compared to the capecitabine only treated patients in the claimed indication.
- In the absence of established efficacy and considering the additional toxicity of the combination treatment, a positive benefit-risk balance has not been established,

the CHMP on the grounds of Article 16 of Regulation 1234/2008/EC has recommended the refusal of the variation to the terms of the Marketing Authorisation.