Annex

Scientific conclusions and grounds for refusal presented by the European Medicines Agency

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Overall summary of the scientific evaluation of Qsiva

- Quality issues

The overall quality of the medicinal product was considered acceptable by the CHMP. There were no outstanding issues on the quality of the active substances, however minor issues remained unresolved regarding the quality of the finished medicinal product: no process validation for the proposed production scale batch size had been performed, therefore the largest batch size that would have been accepted is that of the pilot scale batches. The specification of the finished product was to be revised based on the batch data results and a second identity test method included for each drug substance. Further stability studies on PHEN beads and TPM beads stored in bulk were necessary in order to support a start of the shelf-life at the time of capsule filling. These concerns were raised with the applicant during the procedure but were never adequately addressed.

- Efficacy issues

Treatment with Qsiva 7.5/46 mg and 15/92 mg for 28 and 56 weeks resulted in clinically relevant reductions of body weight, with a maximum effect after approx. 36-40 weeks of treatment. The magnitude of the weight loss was larger compared to previously approved weight reducing agents. The effect was similar in examined subpopulations, but experience in older subjects and patients with cardiovascular disease was very limited.

- Safety issues

Known adverse events with the use of phentermine are palpitations, tachycardia, elevation of blood pressure, psychosis, CNS and gastrointestinal effects and with the use of topiramate paraesthesia, changes in taste, ocular disorders, psychiatric and cognitive disorders. Many of these adverse events were also reported with Qsiva as a fixed-dose combination of phentermine/topiramate in four pivotal Phase III studies and two supportive Phase II studies. There was a dose-dependent increase in the incidence of depression (3.8% in the mid dose group vs. 7.7% in the highest dose group, with 3.4% in the placebo group), anxiety (4.8% vs. 7.9%, respectively, with 2.6% in the placebo group), insomnia (6.8% vs. 10.8%, respectively, with 5.7% in the placebo group), paraesthesia (11.8% vs. 17.3%, respectively, with 1.2% in the placebo group) and cognitive disorders (5.0% vs. 7.6%, respectively, with 1.5% in the placebo group; mainly attention disturbances, memory impairment and language disorders). In the setting of long term use of this product in a large population, the frequency of adverse psychiatric effects and their consequences, as well as the cognitive effects, are unknown.

Phentermine as amphetamine-like substance has a well known drug abuse potential. Topiramate is known as a teratogenic substance causing congenital malformations. Pregnancies have been reported in rather high numbers in the clinical trial program raising concerns with regard to the teratogenic risk of the product when used in a less controlled real life setting. Due to the inhibitory effect of topiramate on renal carbonic anhydrase, reductions in serum bicarbonate below 21 mEq/L were seen in 2.1%, 6.4% and 12.8% in the placebo, mid and high dose groups, and therefore are of concern in the targeted population.

Phentermine's mechanism of action was a concern as it has sympathomimetic properties inducing cardiac stimulation and its use is associated with an increase in heart rate. In the 1 year cohort the frequency of cardiac disorders (mostly palpitations and increase in heart rate) was higher in the Qsiva groups (4.2% and 4.7% in the mid dose and high dose group, respectively) compared to placebo (1.8%). The mean change from baseline to Week 108 in heart rate was also higher in the Qsiva groups (1.3 bpm and 1.7 bpm, respectively) than in the placebo group (0.4 bpm). A meta-analysis of cardiovascular events showed the

population studied to be at a low risk of cardiovascular events. Even though there was no overall signal of an increased risk of cardiovascular events in the studies, the consequences of an increased heart rate in subjects with history of, or with ongoing cardiovascular disease, are unknown. Therefore, the currently available cardiovascular outcome data for Qsiva was considered inconclusive and the long term cardiovascular safety of Qsiva has not been sufficiently established.

Following the CHMP scientific conclusions adopted on 18 October 2012 that Qsiva was not approvable for the treatment of
Obesity, including weight loss and maintenance of weight loss in adults, as an adjunct to reduced calorie diet and physical activity. Qsiva is recommended for obese patients (BMI ≥ 35 kg/m2), or obese patients (BMI ≥ 30 kg/m2) with weight-related co-morbidities such as hypertension, type 2 diabetes or dyslipidaemia. Qsiva should be prescribed by physicians experienced in the management of obesity and obesity-related co-morbidities.
as the safety of the above mentioned medicinal product was not sufficiently demonstrated, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Grounds for re-examination

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) Diabetes Endocrinology with additional experts, inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response. The applicant provided with the grounds for re-examination revised Summary of Product Characteristics (SmPC) and risk management plan (RMP) proposals. The proposed RMP was assessed at the request of the CHMP by the Pharmacovigilance Risk Assessment Committee (PRAC). The applicant presented in writing and at an oral explanation their grounds that the adopted CHMP Opinion may not have considered the data fully and also provided further analyses to support the clinical safety of Qsiva in the proposed indication.

The applicant presented in their submission the following grounds for re-examination:

The applicant emphasised that Qsiva is highly effective in achieving and maintaining weight loss in obese patients, of a magnitude greater than that of any other pharmacological treatment to date with expected improvement of cardiovascular, metabolic, and other outcomes, as well as demonstrated improvements in blood pressure, glycaemic control, lipids, quality of life, incidence of new onset type 2 diabetes and other outcomes. With regard to the general safety profile, the applicant pointed out that Qsiva is a combination of two approved drugs with long histories of use at higher doses and well established safety profiles of both components.

The applicant addressed specifically the CHMP´s four initial principal grounds for refusal:

1. Cardiovascular safety – According to the applicant, the only concern about a potential increase in CV risk arises from a small (1.6 bpm) dose-related increase in heart rate that differed significantly from placebo only with the top-dose, but not for the mid-dose, whereas blood pressure was consistently and significantly reduced by both the mid- and top-doses of Qsiva. Outcomes using various accepted MACE composite endpoints in the Qsiva programme showed no increase in risk for any of these endpoints compared to placebo (hazard ratios <1.0). The applicant further cited supportive CV safety data from published results of clinical studies with other sympathomimetic agents in other indications and from historical data with phentermine.

2. Psychiatric safety – Although there was an increase in reports of psychiatric and cognitive symptoms with the top-dose of Qsiva, the majority of these events were of mild severity, occurred early in treatment, resolved spontaneously or with discontinuation of study drug. Reported rates for most CNS-related side effects were similar between the mid-dose and placebo. Importantly, there were no increases in major depression diagnoses (by PHQ-9 questionaire), emergent antidepressant use, or suicidality (by C-SSRS questionaire) in the programme.

3. Teratogenic risk - Topiramate has been associated with an increased risk of teratogenesis; however, topiramate has been approved for 16 years and is currently in widespread use within the EU for migraine prophylaxis and epilepsy, which requires treatment at higher doses. The Applicant addressed the need for effective contraception and the risk of teratogenesis in the SmPC and the RMP, which included a detailed healthcare provider checklist as well as patient education card. Furthermore, the applicant cited the example of topiramate as further evidence that this risk can be effectively mitigated by SmPC and RMP.

4. The probability of off-label use – A robust SmPC and state-of-the art education-based RMP, further strengthened by the use of comprehensive prescriber checklist and patient education card, was proposed to be put in place by the applicant to be uniformly and easily implementable across all EU countries. In addition, patient registry and drug utilization study was proposed to be conducted to repeatedly evaluate the effectiveness of these measures.

The CHMP considered the following:

In the view of the CHMP an unmet medical need in the treatment of patients with obesity is acknowledged. Qsiva has proven to be very effective in reducing body weight, with a mean weight loss from baseline of approximately 8 and 10% for the mid and high dose, respectively, in the first year. However, no additional weight loss was seen in the second year, rather there was a mean weight gain in all groups. Reduction of weight can be assumed as surrogate parameter for a beneficial cardiovascular (CV) outcome and current EMA guidance on medicinal products used in weight control does not require demonstration of a positive effect on CV morbidity and mortality prior to approval. However, weight reducing agents with a mechanism of action with a detrimental influence on heart rate, such as Qsiva, or on other cardiovascular parameters, may require further exclusion of a harmful CV effect.

1. Cardiovascular safety – The CHMP had methodological concerns with regard to the quality of the data source (with dropout rates of about 40%, and lost to follow up rate above 10%) and the magnitude of the dose-dependent increase in heart rate (as heart rate measurement was not an end point in the Qsiva clinical program and no standardised methodology for accurate assessment was implemented). The Applicant presented hazard ratios for major cardiovascular events in Qsiva-treated subjects. Although these showed no obvious increased frequency of events with treatment, the data are of limited value as the duration of follow-up was relatively short and the total number of events was small. Therefore, the lack of power, and thus reliability, of the post-hoc analysis of cardiovascular events during the Qsiva clinical development program remains a major concern, since with a total number of 1526 patients of low CV risk treated for one year the expected rate of CV events is extremely low and thus of little significance for the assessment of the CV risk. In the view of the CHMP, any increase in heart rate can remain a concern with regard to CV risk. Estimates of the mean heart rate were considered by CHMP not to be necessarily the most relevant parameter (compared to e.g. increase in heart rate in the highest percentile or increased proportion of subjects with > 10 bpm) The consequence of the sympathomimetic mechanism of action of Qsiva for CV outcome in long-term use remains a principle concern for CHMP in the absence of long-term CV outcome trial data. The supportive information on safety of phentermine from the literature provided by the applicant was considered by CHMP to be very limited due to factors such as only retrospective, cohort studies submitted, absence of a reliable control group, etc.. Although the amount of phentermine in the high dose of Qsiva is half of that currently licensed for use as a single agent in the US and the UK, the addition of topiramate was shown to increase exposure to phentermine by 40% in the PK studies. Therefore the cardiovascular effects of Qsiva cannot be implied from data for higher doses of phentermine as a single agent.

2. Psychiatric safety – Depression, anxiety and cognitive impairment were more commonly reported in patients treated with Qsiva than placebo. The collection of psychiatry data with screening instruments such as QPH-9 and C-SSRS was found by CHMP to be inadequate since diagnostic instruments are more powerful and would be needed to reliably establish the clinical relevance and magnitude of the psychiatry adverse events (AEs) observed with Qsiva. Dropout rates for depression with Qsiva significantly outnumbered those

with placebo; thus close surveillance in trials may have stopped progression to more severe symptoms. The applicant's claim that by applying the 3 month stopping rule for non-responders, the number of drop-outs due to neuropsychiatric AEs in the Qsiva group would not exceed those in the placebo group was questioned by CHMP. With regard to reported cases of suicidal ideation in patients treated with Qsiva during the clinical studies, regular assessments in this regard would be required. Another concern was the feasibility to exclude patients with moderate depression from treatment. Overall, the availability of psychiatric expertise at sites of treatment with Qsiva was considered to be necessary by CHMP.

During the re-examination procedure, the applicant proposed a further revised SmPC which forgoes the top dose of Qsiva, associated with the highest rate of psychiatric and cardiovascular adverse events. While the CHMP acknowledged that this could improve the benefit/risk ratio, CHMP concluded that the proposed removal of the high dose from the application did not sufficiently alleviate the concerns of the CHMP both with regard to the psychiatric and cardiovascular safety profile (see points above), which remains for the lower doses. Additionally, the Committee noted that the actual patient numbers treated with the recommended mid dose were limited.

3. Teratogenic risk - CHMP agreed that the risk from the teratogenic potential of Qsiva might be mitigated through the implementation of appropriate risk minimisation measures, which include a Pregnancy Prevention Plan (PPP), the principles of which should be consistent with that agreed across the EU for isotretinoin in 2003. However, it was recognised that effectiveness of the PPP in clinical practice will be difficult to maintain in the long term use.

4. Off-label use - The CHMP considers that Qsiva is expected to have a high probability of off-label use, particularly in patients with some nutritional disorders (e.g. bulimia, Binge Eating Disorder) as well as in psychiatric patients, paediatric populations, adults with high CV risk, and elderly patients. There remains uncertainty whether off-label use can be sufficiently mitigated by the measures proposed by the applicant. The applicant's proposal to retain restricted prescribing (to physicians experienced in management of obesity and/or obesity-related co-morbidities) but to remove restricted distribution and dispensing requirements remained a concern to CHMP as this may still represent a broad prescriber base not limited to specialists. The proposed patient registry was considered a key component to gather long term data on the safety of Qsiva and on the effectiveness of the risk minimisation measures, especially in relation to off-label use. However, due to the voluntary nature of the registry the expected participation was considered to be low and hence its capacity to minimise off-label use remained uncertain.

The CHMP further considered that restricting prescribing to clinical settings where prescribing decisions can be informed by a multi-disciplinary clinical team that can assess both the physical and mental health of the patients and the appropriateness of treatment with Qsiva could help minimise the risks but had concerns about the feasibility of this practice in all EU member states.

Grounds for refusal

Whereas

1. The long term cardiovascular safety of Qsiva has not been sufficiently established. Phentermine's mechanism of action is of concern as it has sympathomimetic properties inducing cardiac stimulation and its use is associated with an increase in heart rate. It is only being approved for short term periods of treatment (less than three months) and its long term cardiac toxicity is unknown. Existing data from phentermine use has major limitations and cannot be extrapolated with regard to conclusions on the safety profile of Qsiva. The proposed removal of the top dose for the use of Qsiva does not alleviate the concerns. The currently available cardiovascular outcome data for Qsiva remains inconclusive;

2. The frequency of adverse psychiatric effects and their consequences, in particular resulting from the topiramate component, is unknown in the setting of long term use of this product in a large population. In

addition, the cognitive effects of such combination during long term treatment remain uncertain in absence of adequate studies;

3. Pregnancies have been reported in rather high numbers in the clinical trial program raising concerns with regard to the teratogenic risk of the product when used in a less controlled real life setting;

4. The probability of off-label use of this product outside the population covered by the claimed indication is expected to be high. There is remaining uncertainty whether the updated risk minimisation measures as proposed by the applicant could effectively prevent such off-label use.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Qsiva.