LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Qsiva
phentermine hydrochloride, topiramate

SE/H/1963/01-04/DC
2019-0868, 2019-0869, 2019-0867, 2019-0866

This module reflects the scientific discussion for the approval of Qsiva. The procedure was finalised on 2020-12-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Vivus BV has applied for a marketing authorisation for Qsiva 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg modified-release hard capsules. The active substances are phentermine hydrochloride and topiramate. Phentermine hydrochloride is an appetite suppressant and topiramate is currently approved for treatment of seizure disorders and migraine.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

The applicant has obtained a product specific PIP waiver from the PDCO/EMA for all subsets of the paediatric population for Qsiva.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The acute anorectic effects of PHEN (phentermine hydrochloride) are well established from non-clinical studies and its clinical use. It is primarily mediated by the central actions of releasing

catecholamine in the hypothalamus involving beta adrenergic and dopamine receptors but not 5-HT receptors. The neuropeptides cocaine-amphetamine-related transcript and neuropeptide Y and the gastro-intestinal peptide cholecystokinin may also be involved. The relative contribution of these mechanisms to the clinically observed activity of PHEN is not known.

TPM (topiramate) has multiple pharmacological mechanisms including modulation of voltage-gated ion channels, potentiation of GABA inhibition, inhibitory effects on kainite/AMPA type of excitatory glutamate receptors, and/or inhibition of carbonic anhydrase (CA) isozymes. One or more of the known pharmacological mechanisms of TPM may contribute to its long-term anti-obesity activity.

The additive activity of PHEN and TPM to decrease body weight was shown in a single study in a rat model of obesity. The body weight reduction in the combination group was significantly greater than in the single agent groups. This information can however not be assessed from the referenced publication which is a poster that do not contain sufficient details of the study. This is accepted, since the anti-obesity effect of QSIVA is assessed based on the clinical documentation.

The pharmacodynamic profile of TPM seems well-characterised in animals, whereas the information regarding secondary pharmacological effects from non-clinical studies of PHEN is sparse.

The VI-0521 clinical program has investigated the effects of VI-0521 on endpoints that characterized its secondary pharmacodynamic profile, including glycemic control, hemodynamics, lipid parameters, inflammation markers, mood and quality of life. See further clinical section.

The use of anorectics has been associated with increased incidence of PPH and valvulopathy. The Applicant claims that there is no evidence of valvulopathy or PPH in association with the use of PHEN alone. This aspect is further addressed in the clinical section.

The structural, pharmacological and neurochemical and profiles of PHEN are similar to that of amphetamine and PHEN has also an abuse potential which has been shown in several animal studies. The documented potential for abuse is further discussed in the clinical section. A warning has been included in the proposed SmPC.

There are no data from non-clinical in vitro or in vivo studies with PHEN on QT effects. A thorough QT/QTc study (OB-118) in healthy volunteers has been undertaken with the combination. There were no indications that the drug combination is associated with QT prolongation. The study is further discussed in the clinical section. No further non-clinical testing is needed.

The experience from the clinical studies with the combination of the two compounds supersede further non-clinical safety pharmacology studies.

III.2 Pharmacokinetics

The methods of analyses have been adequately validated. In rats, overall, PK of PHEN and TPM following co-administration was generally similar to that when dosed alone.

In rat, the exposure to TPM after repeated dosing was higher for females than for males. Further, the Cmax and AUC increased in females after repeat dosing.

In the pregnant female rabbits dosed with a fixed-dose combination of PHEN and TPM, an approximately dose-proportional increase in TPM Cmax and AUC0-24 was observed whereas PHEN increased more than dose-proportionally. PHEN and TPM Cmax were generally similar between gestation day (GD) 6 and GD 18, while a decrease in AUC, -18% – 32%, was noted on GD 18 for TPM.

In dogs dosed with the fixed-dose combination, an approximately dose-proportional increase in TPM Cmax and AUC0-24 was observed while PHEN increased more than dose-proportionally. TPM tmax occurred at 1 h post-dose and t1/2 ranged from 1.8 to 2.9 h. There were no gender-related differences in PHEN or TPM PK in the dog. Following repeated dosing, TPM Cmax and AUC0-24 values decreased (43%).

Co-administration of PHEN and TPM increased the systemic exposure to PHEN by approximately 30-50% in dogs. The increased the systemic exposure to PHEN may be caused by increase in urine pH due to excess bicarbonate excretion related to TPM. However, in rats and female rabbits, comparison of the groups receiving PHEN alone and in combination with TPM suggested no evidence for TPM affecting the exposure to PHEN. In clinical studies (OB-110 and OB-103), PHEN clearance was observed to be decreased in the presence of TPM. No relevant explanation is given by the applicant for the inter species difference of this interaction noted in dogs. In the light of the latter, the applicant was in the first round asked to provide more details and discuss in depth the relevance of these effects. The difference in the phentermine/topiramate drug interaction between rat and dog could be explained by a difference in renal carbonic anhydrase (CA) concentration between these two species. This difference explains that urine pH is higher in rat than in dog. Human and dog urine pH are comparable. Therefore, given similar concentrations of CA in the kidney and a similar acidic urinary pH between dogs and humans, a similar degree of increase in systemic exposure to phentermine was also observed for QSIVA in humans.

Comparison of the groups receiving TPM alone and co-administered with PHEN suggested no consistent evidence for PHEN affecting the absorption and exposure of TPM. A similar comparison of the parameters obtained after administration of PHEN alone versus co-administration with TPM also indicated no substantial or consistent effect of TPM on the exposure to PHEN in rats. A significantly increased exposure was observed in rats and humans after prolonged administration but not in the dogs. The half-life of PHEN and TMP is notably longer in humans than in the animals. The relatively long half-life of PHEN and TMP in humans is most likely due to the low biotransformation compared to that in the rat.

PHEN and TPM exhibited low plasma protein binding. PHEN readily partitions into tissues including the brain and show no signs of accumulation in specific tissues. TPM has low volume of distribution and distributes readily across blood-brain barrier, placenta and milk.

The metabolism of PHEN is based on literature data that is sparse and the applicant provided a discussion regarding the metabolic profile of phentermine in rat, rabbit, dog and human. According to available data N-oxidized metabolic products were formed to about <5% in the urine from human. There is no information about the metabolism of phentermine in the dog but in rat, also used in the repeated-dose toxicity studies, about 3% N-oxidation products were excreted in urine. This indicates that these metabolites also are formed in sufficient amount in plasma. Thus, N-oxidation metabolites are sufficiently covered in these studies. In rabbit, N-oxidized metabolic products accounted for 62% of the dose excreted in urine. There are no known unique human metabolites. See Pharmacokinetic section for further discussion. The metabolism of TPM in vivo is sufficiently described in animals and humans. A gender difference in both PHEN and TPM metabolism was observed in rats. Female rats have lower rates of metabolism compared to male rats, such that PHEN and TPM exposure in females tended to be higher than males. No relationship was observed between PK parameters and gender for either drug in clinical studies.

The major route of PHEN and TPM elimination was through urinary excretion. The rate of PHEN excretion was affected by urine pH. A more acidic pH causes a faster rate of PHEN excretion; a more basic pH causes a decrease in excretion, whereas changes in urinary flow rate had only a slight effect. The ADME characteristics of PHEN and TMP in this combination product are well established and further non-clinical studies are not warranted.

III.3 Toxicology

Repeat-dose studies with the combination of PHEN and TPM were conducted in rats up to 26 weeks and in dogs up to 13 weeks. These studies also contained one group each with the single components. In addition, the Applicant has undertaken a 2 years carcinogenicity study in rats with PHEN, which also provides long-term toxicity data. The Applicant also refers to data for the single components available in the Summary Basis of Approval (SBA). Such data can only be used as supportive evidence, and it is thus of importance that the Applicant has submitted sufficient data to cover normal recommendations for repeat dose toxicity testing to support long-term clinical use. It is considered that the extent of the study program is adequate since there are combination studies of sufficient duration in two species. In addition, there are data for one dose of each component in these combination studies, which together with the supportive evidence from the SBA are considered to sufficiently cover these recommendations. The selection of doses in repeat-dose studies were based on the results from 14 days studies in rats and dogs. However, it is evident that the doses selected for the dog are insufficient to characterise the toxicological profile of this combination product (see below).

In rats, except from expected body weight reduction which occurs already at the low doses the notable findings are increased liver and kidney to body weight ratios (F) at 75 mg/kg TMP (4x (M), 7x (F) clin AUC) and minimal to mild centrilobular hepatocellular hypertrophy (M+F) as well as minimal to mild glandular/non-glandular hyperplasia in stomach (M+F) which also is associated with 11.25 mg/kg PHEN (3x (M), 5x (F) clin AUC). The changes were not observed in the recovery animals. The absolute liver weight decreased significantly in male rats dosed 11.25 mg PHEN which normalised after 4 weeks recovery. High dose TPM was associated with increased liver weights in females which were only partly normalised after the recovery period. The co-administration of PHEN and TPM chronically to rats did not seem to produce any additive or synergistic effects. As also described in the pharmacokinetics section, a gender difference in exposure in the 13-week rat study was observed. The exposure to TPM after repeated dosing was higher for females than for males. Further, the Cmax and AUC increased in females after repeat dosing. The applicant described a common mechanism that could be involved in the observed differences between males and females. The higher exposure to PHEN in females was likely due to cytochrome P450 (CYP) related slower metabolism of PHEN in female rats. A clear description was not provided, however the explanation is plausible.

In dogs, decreased body weight, increased liver weight, and microscopic liver findings was observed at the highest dose 4.5/30 based on these findings the NOAEL was 0.45/3 corresponding to 0.1/0.1 – 0.2X Clin AUC for PHEN and TMP. Exposure margin at HD is only 1X clin AUC. All compound-related effects resolved during the 4-week treatment-free recovery period with the exception of increased relative liver weight in males and there were no corresponding microscopic liver changes in the males. As seen from the TK data, the highest dose tested did only result in same systemic exposure as seen in the clinic, without inducing any marked toxicity. Thus, no margin to clinical exposure was achieved in the 13-week repeat-dose toxicology study. However, the Applicant's justification for dose selection, ie significantly increased weight reduction at higher doses, is considered acceptable and together with the existing clinical experience this supersedes the insufficiency of the study.

The findings in animals administered the PHEN/TPM combination were consistent with those noted in animals administered PHEN as a single agent. The supportive information obtained from the literature (Ionamin SBA) is generally congruent with the results from the studies with the combination product i.e. decreased body weight and effects on liver. Findings reported in the Topamax SBA for TPM were in line with the results obtained in the studies sponsored by VIVUS i.e. reduction in body weight and effects mainly on the liver but also the kidney, which was not observed in the studies by VIVUS.

PHEN and TPM are not considered to be either mutagenic or clastogenic.

The applicant conducted a 2-years carcinogenicity study in rats with PHEN. Exposure at high dose was 11x (M), 15x (F) the clinical dose. No test article-related effects were seen in survival during this 2-year study. As expected, mean body weight was significantly lower in the treated animals than in the vehicle control in males and females in a dose-related manner throughout the study. No effect of

treatment was seen in hematology, macroscopic and microscopic pathology examinations. There were no test article-related differences in neoplastic or non-neoplastic microscopic findings between controls and treated males and females. Granular cell tumor incidence was slightly higher at the higher doses but with no statistical significance when comparing pair-fed and high-dose groups. It can be concluded that the daily oral administration of PHEN for 2 years to Charles River CD rats did not produce any evidence of a carcinogenic effect.

In a mouse carcinogenicity study with TPM (Topamax SBA), tumors of smooth muscle origin in the urinary bladder were seen at oral dosages up to 300 mg/kg. This type of tumors has been reported to be unique to mice. Although the incidence was increased in treated mice, this bladder lesion was also seen in controls. The increased incidence in the treated mice may be secondary to the changes in urine pH produced by CA inhibition. There was no increase in tumors at any dose in either sex in a 2-year study in rats with TPM. Taken together, the findings do not indicate that QSIVA presents a significant carcinogenic risk to the patients.

VIVUS has not performed any fertility and early embryonic development toxicity studies for PHEN, TPM or the combination of the two. In a three-generation reproductive toxicity study in rats with PHEN (Ionamin SBA), PHEN (40 mg/kg) substantially increased mortality and decreased body weight in the parental generation and, for the first and second cycles, produced decreases in the percent of pregnant females, mean live fetuses per litter, mean birth weight, and Postnatal Day 21 survival and pup body weights. In a second rat reproduction study, rats received PHEN orally at 2 and 5 mg/kg/day for a 5-day mating period. No effects were noted on fertility. Fertility studies with TPM were conducted in male and female Sprague Dawley rats (Topamax SBA). The rats were dosed orally via gavage with 0, 0.2, 8, 25 and 100 mg/kg/day. In males, a small increase of testis weight was noted in all dose groups. When treated males were mated to untreated females, increased resorptions and post-implantation losses were noted. In treated females mated to untreated males, post-implantation loss was slightly increased at the top two doses at sacrifice on Gestation Day 13. In treated females, decreased corpora lutea and implantations, increased post-implantation loss and decreased pup weight at birth was noted.

VIVUS has conducted embryo-fetal and pre/post-natal development studies on the PHEN/TPM combination in rats and rabbits; both studies included experimental groups administered either PHEN or TPM as single agents. Results from the study in rats show effects on body weight and increased activity as expected. No evidence of teratogenicity and no effects on maternal macroscopic findings, uterine implantation data, or fetal sex ratios were observed in any group. Margin of exposure was 2-3x clinical dose. In the rabbit study, no effects on maternal Gestation Day 18 blood pH levels, gross pathology, uterine implantation data, fetal sex ratios, and fetal body weights were observed in any treatment group, or on fetal external, visceral, or skeletal evaluations. In the group treated with TPM alone at 25 mg/kg/day, a slight increase in select skeletal aberrations (fused or absent ribs and/or fused, misaligned, malpositioned, absent, or misshapen vertebrae) was noted. These aberrations were noted to have occurred at a similar or higher incidence in the historical control data from the laboratory. However, the margin of exposure for TPM was only 1-2x clin dose in the HD groups. There is no significant drug interaction between PHEN and TPM resulting in teratogenesis at doses tested. Nevertheless, the teratogenic effects of TPM in multiple species, including human are well-established in the scientific literature and the lack of teratogenic effects in the present studies is most likely due to the low exposure to TPM.

In a pre- and postnatal development study (1060-042), rats were dosed on GD 6 and continuing throughout lactation up to and including LD 20. At the 11.25/75 mg/kg/day PHEN/TPM combination dose, test article-related effects in the parental generation animals included an increased activity, salivation, and excessive licking during lactation furthermore lower gestation and lactation weights, lower gestation weight gain, decreased food consumption during gestation and lactation, poor pup survival LD 0-4 (11 females failed to retain viable pups), and maternal neglect as evidenced by an increased frequency of lacerations/wounding and/or cannibalization of the F1 pups early in lactation (LD 0-4). Effects at this dose level in the F1 pups included lower pup body weights at birth and

throughout lactation, delays in the onset of several physical developmental parameters (pinna detachment and eye opening), and delays in sexual maturation. External malformations were also observed in several pups exposed to TPM in the high dose alone or in combination with PHEN. These included forepaw ectrodactyly (3 F) and hindlimb brachydactyly (3 F), tail absent (2 F) or portion absent (1 M), and eye macrophthalmia (1M). The NOAEL for the PHEN/TPM combination treatment to the parental females, their litters, and F1 pups that continued on study was 1.5/10 mg/kg/day. Plasma exposure was not measured in the study. The same dose level as the NOAEL (PHEN/TPM 1.5/10) in the repeat dose toxicity studies, rendered a margin of exposure of <1 for PHEN and 2x for TPM vs the clinical dose.

QSIVA is contraindicated in pregnancy, and in women of childbearing potential if an effective method of contraception is not used.

In the section on Women of childbearing potential, it is stated that WOCBP must use effective contraception during treatment to prevent pregnancy and to continue its use for at least 4 weeks after the last treatment with QSIVA. Four weeks was chosen to cover at least one menstrual cycle and also to provide a large margin for exposure based on half-lives for TPM and PHN.

It is of importance that the presented information in the section regarding pregnancy and the animal studies in section 5.3 in the SmPC should reflect the total knowledge, not only the studies conducted by the applicant. The teratogenic effects of TPM is well established in multiple species. The recommendations from CMDh regarding topiramate was also be taken into consideration. https://www.ema.europa.eu/en/documents/psusa/topiramate-cmdh-scientific-conclusions-grounds-variation-amendments-product-information-timetable/00002996/201701_en.pdf

The Applicant has submitted two juvenile toxicity studies completed in rat. These are not relevant to the current submission as the proposed indication for QSIVA is in adults only. The studies were not assessed.

VIVUS has not conducted phototoxicity studies since TPM and PHEN do not absorb light in the UV/visible range (290 to 700 nm).

III.4 Ecotoxicity/environmental risk assessment

The logP of phentermine was collected from “Exploring QSAR-Hydrophobic. Electronic, and steric constants”. It is not clear if the value 1.9 was experimentally determined and then presented in the table. The Applicant has committed to determine the log Kow of phentermine experimentally. The report and updated ERA are expected no later than end of 2Q 2021 (Post approval commitment).

The partition coefficient for topiramate is determined according to OECD 107 in a non-GLP study to be 0.54 (or 0.51 as stated in the report). This is acceptable.

The Phase I PECSURFACE WATER for phentermine hydrochloride (0.075 µg/L) and topiramate (0.46 µg/L) are above the action limit of 0.01 µg/L. A Phase II risk assessment is thus triggered for both components. The applicant has presented a table of ongoing studies for the Phase II risk assessment. The selection of studies is acknowledged with the addition that the readily biodegradability of both compounds should be determined according to OECD 301. The OECD 301 study can be waived in Phase IIA if OECD 314b or OECD 308 is performed (but not in Phase IIB for PECSW refinement purposes).

The Phase II risk assessment is ongoing and will be submitted post approval. In addition to the proposed list a study on biodegradability according to OECD 301 (or OECD 314b or OECD 308) should be submitted. The Applicant has informed that further delays in the timetable for the studies is expected. The updated ERA is expected no later than end of 2Q 2022.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The pharmacokinetics of phentermine and topiramate as a fixed combination product has been investigated in a total of 10 studies in healthy obese subjects and in 5 studies in patients. A total of 606 subjects were included and evaluated in the phase I studies.

Two population PK reports were provided. The demographic factors weight, creatinine clearance, age, gender and race were explored for influence on pharmacokinetic parameters.

The analytical methods employed appears properly validated.

Absorption

After oral administration of the PHEN/TPM capsules maximum plasma concentrations were reached within approximately 6 hours for phentermine (range 3-7 h) and for topiramate 9 hours (range 7-12 h). The absolute bioavailability of phentermine has not been determined. The absolute bioavailability of topiramate has been reported to be 81-95 % for the European reference product (Topamax). Bioequivalence of the applicant´s fixed combination formulation with commercially available single component products (Adipex-P (phentermine, US-market only) and Topamax (topiramat)) has been established regarding extent of exposure. Bioequivalence between commercial formulation and the formulation used in pivotal phase III studies has been established for both active substances.

An in vitro study in Caco-2 cells indicate that permeability of phentermine is high and that it is not a substrate for P-gp. Based mainly on one reference the Applicant states that topirmate is not a p-gp substrate.

After intake of high-fat food, no significant food effect was observed (10 % decreased Cmax of topiramate with high fat food). The product may be taken with or without food.

Distribution

The mean oral volume of distribution (V/F) of phentermine and topiramate following a single oral dose of PHEN/TPM 7.5 mg/46 mg is stated to be 252 litres and 14 litres, respectively. The protein binding is in the range of 18 % for phentermine. No investigation of any pH–dependent or concentration dependent binding was performed by the applicant. The protein binding for topiramate is 13-17 %. Based on literature, it is stated that topiramate binds to a high-affinity low capacity saturable erythrocyte-binding site.

Elimination

The applicant has provided a very brief summary of the metabolism and excretion of phentermine. The majority of the dose (for both phentermine and topiramate) is excreted unchanged in urine, 70-80 % for phentermine and 70 % for topiramate. The rate of phentermine excretion is increased in acidic urine and decreases in alkaline urine. For phentermine, 3-4% and < 5% of the administered dose was excreted in human urine as p-hydroxylated and N-oxidation products, respectively. Information on the levels of phentermine metabolites in plasma is lacking. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of phentermine is CYP3A4. Six metabolites of topiramate formed via hydroxylation, hydrolysis and glucoronidation have been identified in humans, none of which constitutes more than 5% of an administered dose. The apparent oral plasma clearances (Cl/F) are approximately 26 and 148 ml/min for topiramate and phentermine, respectively. Phentermine and topiramate apparent terminal half-lives (t½) were around 20 and 65 hours,

respectively. The renal clearance of topiramate is in the range of 10-20 ml/min. Since fu x GFR is much higher than this value, there is no indication that active secretion is a major process in topiramate elimination. No measure of renal clearance for phentermine has been provided.

Dose proportionality and time dependency

The pharmacokinetics of phentermine and topiramate appears to be approximately dose and time proportional. Steady state of both phentermine and topiramate is expected after approximately 3-4 and 8 days of administration, respectively. In the single- and multiple-dose study OB-102, single-dose PK was assessed with samples collected over a 96-hour period. Subjects were then treated for 21 days with an accelerated dose titration, and steady-state pharmacokinetics were assessed at the end of treatment. The accumulation ratio of phentermine is somewhat higher than expected based on the estimated t½ and once daily dosing (2.5- to 2.9-fold compared to the expected 2-fold accumulation for AUC and Cmax). The accumulation of topiramate was somewhat higher than expected, being 3.7-fold at the high dose and 5.2-fold at the low dose (expected 2.9- to 3.1-fold).

Special populations

In patients with mild and moderate hepatic impairment there was an approximate 40 and 60 % increased exposure of phentermine respectively as compared to healthy subjects. Patients with severe hepatic impairment have not been investigated.

For both phentermine and topiramate, the exposure increased approximately two-fold in subjects with severe renal impairment as compared to healthy subjects. In subjects with moderate renal impairment, the exposure increase was 85 % for topiramate, whereas it was 45 % for phentermine. In subjects with mild renal impairment, the increase was less, being in the range of 25 % for both active substances. There is no information on the pharmacokinetics of PHEN/TPM in patients with end stage renal disease.

Renal impairment was also investigated using the popPK models. Based on simulations, subjects with normal renal function, increases of 150%, 59%, and 24% in plasma AUCss of exposure to phentermine and 134%, 59%, and 25% in plasma AUCss of topiramate were predicted in patients with severe, moderate and mild renal impairment, respectively. The dosing in RI patient as well as simulations comparing exposure in patients with normal renal function and patients with severe RI are shown below.

Table 1 Dosing recommendations for patients with renal impairment

Dosing of QSYMIA	Renal impairment:		
	mild	moderate	severe
Starting dose	3.75 mg/23 mg daily	3.75 mg/23 mg daily	3.75 mg/23 mg every other day
Dose adjustments	Increase to 7.5 mg/46 mg daily at Month 3 is possible if well tolerated and BMI > 30 kg/m^2	none	At Day 14, increase to 3.75 mg/23 mg daily possible if well tolerated
Maintenance dose	3.75 mg/23 mg daily or 7.5 mg/46 mg daily	3.75 mg/23 mg daily	3.75 mg/23 mg every other day or 3.75 mg/23 mg daily
Maximum dose	7.5 mg/46 mg daily	3.75 mg/23 mg daily	3.75 mg/23 mg daily

Table 4 Average concentrations of phentermine and topiramate at steady state predicted for patients with normal renal function and with renal impairment at the recommended dose levels

Dosing Frequency	Dose levels	Mean (coefficient of variation) Average concentrations (Phentermine [ng/mL], Topiramate [µg/mL])			
		Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment
Every other day	Phentermine 3.75 mg				24.2 (36.8%)
	Topiramate 23 mg				0.843 (27.2%)
Once daily	Phentermine 3.75 mg	19.0 (35.4%)	23.6 (33.8%)	30.3 (34.7%)	47.5 (37.2%)
	Topiramate 23 mg	0.706 (29.0%)	0.883 (28.9%)	1.13 (28.5%)	1.66 (27.6%)
	Phentermine 7.5 mg	38.0 (35.4%)	47.2 (33.8%)		
	Topiramate 46 mg	1.41 (29.0%)	1.77 (28.9%)		
	Phentermine 11.25 mg	57.0 (35.4%)			
	Topiramate 69 mg	2.12 (29.0%)			
	Phentermine 15 mg	76.1 (35.4%)			
	Topiramate 92 mg	2.83 (29.0%)			

Paediatric population
No investigation of the pharmacokinetics in children has been made.

Interactions
In vitro studies
The potential of phentermine to inhibit CYP2C19, 2B6 and 2C8 was investigated at a single concentration of 10 µM (15-fold unbound Cmax). No significant inhibition was observed. For topiramate, inhibition of CYP2C8 was investigated with a concentration of 100 µM (8-fold unbound Cmax) and a 16% inhibition of CYP2C8 was observed.

In study 101-09-001, the induction potential of phentermine was evaluated for 48 hours at three concentrations, 0.3, 1 and 10 µM. The investigated enzymes were CYP1A2, CYP2B6 and CYP3A4. The induction was measured at activity level and not at mRNA level. Compared to the control response, the induction response ranged from 90 % to 144 % for CYP1A2, from 91 to 165 % for CYP2B6 and from 70-114 % for CYP3A4.

The purpose of study OPT-2012-105 was to determine whether phentermine, topiramate and the combination of phentermine and topiramate inhibit the transport of the probe substrates of the human transporters OAT3, OAT4, OCT2, OCT3, MATE1 and MATE2-K. Phentermine was studied in the concentration range of 0.03 – 10 µM and topiramate was studied in the concentration range of 0.3 – 100 µM. For phentermine the IC50 value for OCT2 was determined to be 0.971 µM. For topiramate the IC50 value for MATE2-k was estimated to be 90.1 µM. Due the lack of sufficient inhibition, the IC50 values couldn't be determined for any other transporter. The combination of phentermine and topiramate did not inhibit any transporter sufficiently to determine a IC50 value.

In vivo studies
The potential for drug-drug interaction between the two components of the FDC was evaluated in two different studies, OB-110 and OB-103. The interaction effect by topiramate on phentermine was comparable between two studies (42 % versus 33 % increased exposure of phentermine). The interaction has not been studied at steady state. This interaction is likely due to the known inhibition of

carbonic anhydrase by topiramate, resulting in alkalinised urine and increased re-absorption of phentermine.

The steady-state PK of phentermine, topiramate, sitagliptin, and metformin when administered alone and in combination in healthy subjects; and the effect of a single oral dose of 2 g probenecid on the multiple-dose PK of phentermine and topiramate has been evaluated. The pharmacokinetic parameters of phentermine and topiramate were not altered upon co-administration with metformin, sitagliptin or probenecid. Metformin Cmax and AUC were increased 16 and 23 % respectively. Sitagliptin Cmax and AUC were not altered upon co-administration.

Upon co-administration with PHEN/TPM, the ethinyl estradiol Cmax and AUC were decreased by 8 and 16 %, respectively. The norethindrone Cmax and AUC were increased by 22 and 16 %, respectively. The interaction with ethinyl estradiol is in line with previously observed results for topiramate.

In Study OB-404 the primary objective was to evaluate the effects of PHEN/TPM on glomerular filtration rate (GFR), as measured by iohexol clearance; and to distinguish these effects from changes in creatinine-based estimates of GFR. The observed consistency between creatinine-based estimates of GFR and estimates based on iohexol clearance would indicate that observed increases in sCr in subjects treated with PHEN/TPM are the result of commensurate reduction of GFR, rather than inhibition of tubular creatinine secretion. Had inhibition of OCT2 and MATE2-K been the primary cause of sCr increases observed in-vivo, iGFR reductions would not be expected to occur. Inhibition of OCT2 and MATE2-K can however not be completely excluded.

Final popPK models

The previous population PK models of phentermine and topiramate were updated with PK data collected in a total of nine studies, including four Phase I studies (OB-102, OB-103, OB-105 and OB-106), two Phase II studies (OB-202 and DM-230) and three Phase III studies (OB-301, OB-302 and OB303). The updated population PK model included the administration of phentermine and topiramate as monotherapies or combination therapy.

Discussion on Clinical Pharmacology

The pharmacokinetic profile of topiramate is well known, products have been in clinical use on the EU market since 1996. Adequate references have been provided to support the literature based topiramate-data.

The pharmacokinetics of phentermine is less well studied, although a known active substance within the EU where several approved products containing phentermine have been marketed for different time periods. In the US approved products containing 30 mg phentermine has been in use since 1959 and QSIVA was approved by the FDA in 2012. The current application has deficiencies in the description of phentermine's pharmacokinetic profile. There is no information on the levels of metabolites in plasma. However, phentermine has been in use for a long period (approximately 60 years at double the maximum dose of QSIVA). Phentermine is mainly excreted unchanged in the urine (75-85%). The levels of metabolites in urine is similar or lower in humans than the preclinical species and there is likely no human specific metabolite with major relevance. Overall, the provided information can be considered acceptable in this particular case.

The in vitro studies submitted by the Applicant are not in line with the current Guideline on the investigation of drug interactions. All studies were performed before this guideline came into effect.

Further in vitro studies to fully characterize the interaction potential of phentermine, in line with the current guideline, were requested at day 70, but not provided by the Applicant. Instead the Applicant has agreed to perform additional in vitro studies and provide the results within 12 months of market approval. The studies planned by the Applicant will cover the deficiencies (compared to the current guideline) in the already performed in vitro studies.

The exposure of phentermine was increased by 37 and 60 % for subjects with mild and moderate hepatic impairment as compared to healthy subjects. The observed results are surprising given the stated high renal excretion of unchanged phentermine. The Applicant has proposed renal tubular acidosis (RTA), a defect in urinary acidification, which has been found in 21- 45% of chronic liver disease patients as a possible explanation. RTA, making the urine alkaline, would increase the reabsorption of phentermine and hence increase its exposure. Since it is not known whether the subjects included in the specific study were diagnosed with renal tubular acidosis, the explanation remains hypothetical.

The phentermine popPK model includes CrCL and Age covariate effects on CL/F. CrCL and age are correlated. The applicant was asked to test a model with only CrCL and discuss if age covariate is appropriate to keep in the model or not. The results indicate that there was no relevant difference between models with and without age since the estimate of clearance did not change much and conclusions would be the same. Thus, the proposed final model for phentermine including age and CrCL is accepted.

The exposure of both phentermine and topiramate was increased in subjects with renal impairment. The provided simulations for patients with normal renal function and renal impairment support the proposed posology.

IV.2 Pharmacodynamics

Qsiva is a combination of phentermine and topiramate. Both substances suppress appetite but with different mechanisms.

The primary mechanism of action of phentermine producing weight loss is believed to be pharmacologically induced caloric intake reduction through the stimulated release of norepinephrine. Scientific literature postulate that increased circulating catecholamines may cause appetite suppression by increasing blood leptin levels. Increased norepinephrine levels may also result in a decrease in neuropeptide Y production, which may result in increased satiety and decreased appetite. Phentermine has no central or peripheral effect on serotonin (5-HT).

Available pharmacological evidence suggests that topiramate-induced weight loss may result from increased satiety due to decreased gastrointestinal motility, increased energy expenditure and decreased caloric intake.

IV.3 Clinical efficacy

Beneficial effects

The PHEN/TPM clinical development program on body weight and other metabolic factors included four pivotal phase 3 studies (OB-301, OB-302, OB-303, and OB-305) and five phase 2 studies (OB-201, OB-202, DM-230, DM-231, and OB-204). The duration of the studies was 28 and 56 weeks, while subjects included in study 305 was followed for a total of 108 weeks. Study 3025 was an

extension of one of the 1-year studies. Both patients with and without weight-related co-morbidities were studied as well as patients morbid obesity.

Mean percentage weight loss from baseline in the pivotal studies was approximately 8 and 10 % at week 56 for the 7.5/46 mg and 15/92 mg dose, respectively, compared to 1.2-1.8% weight loss in placebo groups. Approximately, 62% and 67% reached at least 5% weight loss, and 38% and 45% reached 10% weight loss, with the two doses, respectively compared with 15-30 % and 7-11%, respectively, in the placebo groups. The magnitude of the weight reduction was independent of gender, BMI and co-morbidities, such as diabetes and hypertension.

There are no indications of a detrimental effect of PHEN/TPM on weight related cardiovascular risk factors, but rather a beneficial effect on blood pressure, glucose and lipids.

Uncertainties in the knowledge about the beneficial effects

The experience in subjects older than 70 years is limited which is reflected in the product information. The majority of the subjects had baseline BMI between 30 and 40 kg/m2. The experience in patients with BMI <30 kg kg/m2 is limited, but there does not seem to be any major differences in effect based on baseline BMI.

In most of the pivotal studies, the drop-out rates were rather high and discontinuations due to adverse events was most common in the group receiving the combination PHEN/TPM 15/92 mg. The robustness of results regarding their clinical relevance and statistical significance under conservative assumptions is accepted. The pivotal phase 3 studies were exclusively performed in US centres, but the potential differences compared to an EU population (e.g. diet) is not expected to influence the effect of the treatment.

No randomization was performed in study 305, but treatment allocation was based on study OB-303. Since 676 of 866 (78%) eligible patients from study OB-303, i.e. 676 of 2,487 (27%) randomized patients, decided not to participate in study OB-305. Therefore, randomization of study OB-303 was likely to be broken resulting in an increased risk of uncontrolled confounding factors.

IV.4 Clinical safety

Unfavorable effects

Known adverse events with the use of phentermine are cardiovascular effects (palpitations, tachycardia, elevation of blood pressure, ischemic events), CNS effects (headache, dizziness, insomnia, psychosis) and GI adverse events (dry mouth, diarrhoea, constipation). Moreover, phentermine as amphetamine-like substance has a known drug abuse effect. With topiramate monotherapy, CNS effects and psychiatric disorders such as paraesthesia, depression, anxiety, somnolence and cognitive disorders have been commonly reported. Ocular disorders (diplopia, visual disturbances) have also been frequently reported. Topiramate is known as a teratogenic substance causing congenital malformations.

Many of these adverse events were also reported with the fixed-dose combination of PHEN/TPM, but there is no indication that any of these are aggravated compared to what is seen for the mono components. Furthermore, the doses in the fixed-dose combination are considerably lower compared to the doses approved for the single components.

The incidence of *psychiatric disorders*; anxiety (4.6%, 4.8% and 7.9% vs 2.6%), depression (5.0%, 3.8% and 7.7% vs 3.4%) and sleep disorders (6.7%, 6.8% and 11% vs 5.7%) was increased for the QSIVA 3.75/23 mg, 7.5/46 mg and 15/92 mg groups vs the placebo group. Overall, the highest incidence was identified for the highest dose group, PHEN/TPM 15/92 mg. However, none of the events were serious. Drug discontinuation due to anxiety (25% vs 15%), depression (23% vs 7.5%) and sleep disorder (13% vs 7.9%) was higher for QSIVA vs placebo.

Approximately 28% of subjects reported a history of any psychiatric disorder at baseline and 21% had a history of depression; although, the PHQ-9 score indicated 'no clinical depression' for the majority (74-77%) of subjects across the groups and 'mild depression' for 18-22% of the subjects at baseline. The incidence of depression was greater in those patients with a history of depression than in patients without a history of depression (for the 15/92 mg dose; 11% vs 6.8%). However, the relative risk of incident depression with the 15/92 mg dose compared with placebo was 1.73 in subjects with a history of depression and 2.72 in subjects with no history of depression. Therefore, a history of depression cannot be used to sort out subjects at a higher relative risk of treatment-induced depression.

Cognitive disorders such as attention disturbances (2.0% and 3.5% vs 0.6%), memory impairment (1.8% and 2.5% vs 0.6%) and language disorders (0.6% and 1.2% vs 0.1%) was dose-dependently increased with PHEN/TPM treatment 7.5/46 mg and 15/92 mg dose compared to placebo. None of the events were serious.

Paraesthesia was a common adverse event in subjects exposed to QSIVA (14% and 20% vs 1.9% for PHEN/TPM 7.5/46 mg and 15/92 mg, respectively, vs placebo).

There was a higher proportion of subjects with *cardiac disorders* (mostly palpitations and increased heart rate) in the PHEN/TPM groups compared to placebo; 4.2% and 4.7% for the mid and high dose group vs 1.8% for placebo. The mean change in heart rate was 0.6 bpm and 1.6 bpm vs 0.0 bpm for mid and high dose PHEN/TPM groups vs placebo. The proportions of subjects with an increase in heart rate > 10bpm from baseline at any time point during the studies was 50% and 56% vs 42% for mid and high dose PHEN/TPM groups vs placebo.

The meta-analysis of CV events in the pivotal studies indicated no obvious increased frequency of major cardiovascular events with PHEN/TPM treatment; however, the duration of follow-up was relatively short. The studied population was at rather low risk since subjects with high cardiovascular risk were excluded from the clinical studies. In addition, the incidence of CV outcome events has been analysed in one completed retrospective register study (OB-905) performed after approval of PHEN/TPM in the US. The rate of major adverse cardiovascular events (MACE) was not increased for phentermine/topiramate and phentermine users, respectively, but was unexpectedly increased for topiramate. Topiramate is not associated with increased heart rate but on the opposite, has demonstrated bradycardia and hypotension. The increased risk of MACE in the group of topiramate users in study OB-905 seems to be driven by the increased risk of stroke. It is acknowledged that slightly more subjects in the topiramate group, compared to the group of unexposed former users, had a history of stroke; however, the differences were small. The results from the performed OB-905 study should be interpreted with caution since the number of events was small, the confidence intervals were overall wide, and the average exposure time (2-2.5 months) was rather short.

The *teratogenic potential* of topiramate is known. Preclinical studies have shown reproductive toxicity for topiramate. Data from published pregnancy registries and observational studies indicates that exposure to topiramate during the first trimester of pregnancy appears to be associated with an

increased risk of oral clefts. QSIVA is proposed to be contraindicated in pregnancy and in women of childbearing potential not using effective forms of contraception.

Due to the inhibitory effect of topiramate on renal carbonic anhydrase, *reductions in serum bicarbonate* were observed. About 16%, 22% and 30% vs 5.9% in the low, mid and high dose PHEN/TPM groups vs placebo had decreases <21 mEq/L in serum bicarbonate, at any time observed. However, only about 2 % had serum bicarbonate <17 mEq/L. Metabolic acidosis could cause hypercalciuria which could contribute to calcium formation and nephrolithiasis. Moreover, low serum bicarbonate may be of concern in obese, diabetic patients treated with metformin, who are already at risk for lactic acidosis. The decrease in serum bicarbonate and the risk of metabolic acidosis and the risk of nephrolithiasis have been reflected in the SmPC.

QSIVA can cause an increase in serum creatinine that reflects a decrease in renal function (glomerular filtration rate). Measurement of serum creatinine prior to starting QSIVA treatment and before increasing the QSIVA dose is recommended.

Uncertainties and limitations about unfavourable effects

The major safety concerns are the increased risk of *cardiac arrythmias* (mainly palpitations and increased heart rate), *psychiatric events, cognitive disorders,* and *teratogenicity* with PHEN/TPM treatment.

The safety-related issues were dose-dependent, and the incidence of cardiac disorders, psychiatric, disorders and cognitive disorders were considerably higher for the highest dose (15/92 mg) compared to the mid dose (7.5/46 mg) dose. However, there was no difference in the incidence of serious adverse events.

The impact of an increase in heart rate in patients with CV disease and/or early stages of heart failure is not known since these patients were not included in the clinical studies. There is no overall signal of an increased risk of CV events in the studied population. However, there are uncertainties considering use in populations at higher CV risk. Therefore, the consequences of an increased heart rate in subjects with history of, or ongoing cardiovascular disease is unknown. Considering the beneficial effect on other CV risk factors, the potential risk associated with an increase in pulse rate is considered as acceptable provided that the SmPC and the educational material includes adequate information.

Phentermine has been associated with valvular regurgitation and pulmonary hypertension. However, phentermine has not been associated with central or peripheral effects on serotonin (which is considered as the mechanism behind these adverse events), and no observation of cases of valvular regurgitation and pulmonary hypertension has been reported with the phentermine/topiramate fixed combination in the clinical studies.

Educational material (prescriber guide and checklist/patient guide) has been proposed to address pregnancy prevention, increased heart rate, psychiatric disorders and cognitive disorders. Draft key messages have been updated accordingly.

A registry study (OB-906) is planned to evaluate effectiveness of the implemented risk minimisation measures and thus if exposure during pregnancy has occurred. The observational study OB-907 will evaluate the effectiveness of risk minimisation measures in place to minimise risk of psychiatric disorders and risks in relation to effects on heart rate, namely if the warnings and precautions in the SmPC, regarding CV and psychiatric history, are followed before prescribing QSIVA.

Considering the adverse event profile, QSIVA should be intended for use under the guidance and supervision of physicians familiar with the treatment of obesity. This has been stated in the SmPC (4.2).

Phentermine has an *abuse potential* that cannot be overlooked. The risk of drug abuse cannot be overseen. A warning has been included in the proposed SmPC.

The experience in *elderly* is limited since all phase III studies included adult subjects <70 years of age. Overall, 254 subjects were ≥65 years of age of which 156 were on treatment with QSIVA. This has been reflected in the SmPC.

No safety data have been provided in *subjects with renal impairment* or *in subjects with hepatic impairment*. Exposure in patients with impaired renal function is increased and, therefore, reduced doses are proposed in this subgroup.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to QSIVA.

Safety specification

The presentation in SI-SVI of the Safety Specification is largely acceptable. The Summary of safety concerns in the table below.

Table 1 Summary of safety concerns as proposed by the Applicant

Important identified risks	Cognitive impairment (TPM)
	Psychiatric disorders (depression/anxiety, including suicidal behaviour and ideation) (TPM/PHEN)
	Teratogenicity (TPM)
	Elevations in serum creatinine (TPM)
Important potential risks	Serious cardiovascular risks (PHEN)
Important missing information	Elderly > 70 years
	Patients at high cardiovascular risk

Conclusion on the Safety Specification by the RMS

The safety specification as proposed by the Applicant is endorsed.

Pharmacovigilance Plan

The Applicant has submitted draft synopsis, including milestones for protocol submission, interim data and the final reports, have been submitted for study OB-906 and OB-907, respectively. Protocols will be submitted within 3 months of the finalised procedure.

Plans for post-authorisation efficacy studies

N/A

Risk minimisation measures

Educational material (prescriber guide and checklist/patient guide) has been proposed to address pregnancy prevention, increased heart rate, psychiatric disorders and cognitive disorders. Draft key messages have been updated accordingly.

Summary of the Risk Management Plan

The Summary of the RMP, Part VI, has been updated accordingly.

The submitted Risk Management Plan, version 06 is considered acceptable.

IV.6 Discussion on the clinical aspects

Overweight and obesity are recognized as disease states that often are associated with comorbid conditions. In general, health risks increase with severity of overweight and obesity and include hypertension, dyslipidaemia, insulin resistance, type 2 diabetes mellitus and cardiovascular disease. Other symptoms and disease states that are related to overweight and obesity, such as sleep apnoea, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations can also severely impair patients' health and quality of life. Weight reduction has been associated with beneficial effects on cardiovascular risk factors, such as blood pressure and lipid profiles, as well as improved glycaemic control in both patients with and without type 2 diabetes. Relevant decreases in certain risk factors associated with overweight and obesity have been seen with loss of 5 to 10% of initial weight. Thus, weight reduction in obese and overweight subjects is considered as an important goal to prevent both cardiovascular and non-cardiovascular comorbidities.

First line treatment should always be dietary measures and physical exercise, but when these measures do not result in adequate weight reduction, pharmacological treatment is needed. The effects of PHEN/TPM on body weight related endpoints as well as the effect on blood pressure, serum lipids and glucose parameters are considered to be of a magnitude that can reduce CV risk. It could also be expected that treatment would lead to beneficial effects also on non-cardiovascular related complications such as sleep apnoea, joint pain, urinary incontinence, impaired fertility and functional limitations even though this has not been specifically studied. The weight reducing effect has not been compared to other approved weight reducing agents, but the magnitude of the effect is at least as high as the one documented for e.g. sitagliptin and orlistat based on comparisons between studies.

The adverse event profile of PHEN/TPM is reflecting the known mechanism of topiramate and phentermine, but there are no indications of additive toxicity. Further, the doses of the separate compounds are considerably lower compared to the approved mono-components.

An increased incidence of psychiatric adverse events, in particular depression and anxiety, was documented for the highest dose, while the difference between the mid dose and placebo was less pronounced. This is reflected in the SmPC section 4.4. Patients with a history of or concurrent mood disorder or depression should be evaluated carefully to ensure treatment with QSIVA is warranted. Treatment with QSIVA is not recommended in patients with a history of recurrent major depression, bipolar disorder, or psychosis, or in patients with current depression of moderate or worse severity.

As expected, based on the mechanism of action of phentermine, there was an increase in heart rate in the pivotal studies and in the QT-study. The mean increase in heart rate was not substantial and not

associated with increase in blood pressure. Instead, a beneficial effect on blood pressure was documented which, in conjunction with a reduced body weight, is expected to outweigh the limited negative effect on hear rate. However, there are uncertainties concerning use in high risk populations with CV disease and/or early stages of heart failure since these patients were not included in the clinical studies. Use of QSIVA is not recommended for patients with a recent myocardial infarction (< 6 months) or in other patients at high cardiovascular risk including those with a history of advanced cardiovascular disease. Recommendations to monitor heart rate is included in the SmPC.

Even though it is acknowledged that topiramate is already approved in the EU, the known teratogenic potential of topiramate is of serious concern in the context of the target population, consisting to a large extent of fertile women. Measures to avoid pregnancy are of outmost importance. QSIVA is proposed to be contraindicated in pregnancy and in women of childbearing potential not using effective forms of contraception, and the teratogenic risk is included in the RMP. Additional risk minimisation measures in terms of educational material (prescriber guide and checklist and patient guide) to address pregnancy prevention and the risk of increased heart rate, psychiatric disorders and cognitive disorders has been proposed. Furthermore, two studies are planned to evaluate effectiveness of the implemented risk minimisation measures on pregnancy prevention (OB-906) and the risk of psychiatric disorders and risks in relation to effects on heart rate (OB-907).

Considering the adverse event profile, QSIVA should be intended for use under the guidance and supervision of physicians familiar with the treatment of obesity.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was German.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

A clinically relevant weight reducing effect that is expected to reduce the risk of weight related comorbidities has been documented for PHEN/TPM in all weight strata.

The safety profile of the product includes an increased risk of psychiatric disorders, cognitive disorders and teratogenicity. These risks should be carefully considered before initiating treatment with Qsiva, in particular the risk of teratogenicity considering that the expected target population will include women of childbearing potential. A pregnancy text must be performed before initiating treatment and adequate contraception must be applied during treatment.

The risk of depression is also of relevance in the target population. The risk was most pronounced with the highest dose.

The risks are reflected in the SmPC as well as in the proposed education material. Educational material to prescribers and patients has been adequately proposed for pregnancy prevention and the risk of increased heart rate, psychiatric disorders and cognitive disorders.

The dose-dependent increase in adverse events may question the need for the high dose. However, there was no increase in serious adverse events, and it is recognized that patients with a BMI above 30

after 3 months treatment with the mid dose may benefit from the higher dose (provided that tolerability is acceptable) to reduce the risk of CV events.

Even if the experience in patients with a BMI below 30 is limited, available data support a similar effect in this group compared to the total study population. Thus, the proposed target population (adult patients with an initial Body Mass Index (BMI) of ≥30 kg/m², or ≥27 kg/m² with weight-related co-morbidities such as hypertension, type 2 diabetes or dyslipidaemia) is acceptable.

In conclusion, the benefits are considered to outweigh the risks.

The benefit/risk ratio is thus considered positive and Qsiva 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg modified-release hard capsules is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post approval commitments

Description	Due date
In vitro studies of time dependent inhibition of CYP-enzymes for both phentermine and topiramate	In 2021
In vitro CYP induction experiment using mRNA endpoint for phentermine	In 2021
In vitro studies investigating the potential of phentermine to inhibit P-gp, BCRP, OATP1B1, OATP1B3, and OAT1	In 2021
In vitro studies investigating the potential of topiramate to inhibit BCRP, OATP1B1, OATP1B3, and OAT1	In 2021
ERA: Experimentally derived log Kow of phentermine. Report and updated ERA	End of Q2 2021
ERA: Phase II risk assessment. Updated ERA.	End of Q2 2022

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
A registry study to evaluate effectiveness of the implemented risk minimisation measures and thus if exposure during pregnancy has occurred. Protocol will be submitted within 3 months of the finalised procedure.	Interim (3-year data) and final (7-year data) reports
An observational study to evaluate the effectiveness of risk minimisation measures in place to minimise risk of psychiatric disorders and risks in relation to effects on heart rate, namely if the warnings and precautions in the SmPC, regarding CV and psychiatric history, are followed before prescribing QSIVA. Protocol will be submitted within 3 months of the finalised procedure.	Interim (1- and 3-year data) and final (7-year data) reports

- **Additional risk minimisation measures (including educational material)**

The educational material should contain the following key elements:

Prior to the use of QSIVA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at informing prescribers of the relevant data to collect and parameters to monitor to ensure patients safety on the one hand and educate patients with regards to important risks on the other hand.

The MAH shall ensure that in each Member State where QSIVA is marketed, all healthcare professionals and patients/carers who are expected to prescribe/use QSIVA have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Prescriber guide and checklist
  - **Prescriber guide and checklist**:
    - Check for eligibility, contraindications and warnings
    - Check for possible drug-drug interactions
    - Check for treatment allocation, initial and subsequent treatment adjustments
    - Pregnancy test
    - Check for compliance with contraception requirements
    - Check for solicited adverse reactions, depression/suicidality, cardiovascular or cognitive events

The patient information pack:

- Patient information leaflet
- A patient/carer guide
  - **Patient/carer guide**:
    - A description of the teratogenic risk associated with the use of QSIVA namely: oral clefts
    - Description of the need for contraception
    - A description of the correct use of QSIVA and the risks associated with its use, namely: Depression/anxiety and potential risk of cardiovascular or cognitive events
    - Remarks on the importance of reporting on specific adverse reactions, namely: Chest pain; fast or uneven heartbeat; unusual thoughts, mood or behaviour; anxiety, or depression; attention, memory and language/word-finding difficulties.

A warning that patients should avoid driving or operating heavy machinery until they know how QSIVA affects them

VII. APPROVAL

The decentralised procedure for Qsiva 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg modified-release hard capsules was positively finalised on 2020-12-22.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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