Part VI: Summary of the risk management plan

Summary of risk management plan for Qsiva (Phentermine/Topiramate)

This is a summary of the risk management plan (RMP) for Qsiva. The RMP details important risks of Qsiva, how these risks can be minimised, and how more information will be obtained about Qsiva 's risks and uncertainties (missing information).

Qsiva 's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Qsiva should be used.

Important new concerns or changes to the current ones will be included in updates of Qsiva's RMP.

I. The medicine and what it is used for

Qsiva is authorised for obese patients (BMI ≥ 30 kg/m^2), or overweight patients (BMI ≥ 27 kg/m^2) with other health problems caused by their weight such as high blood pressure, diabetes or abnormal levels of fats (lipids) in the bloodstream. In conjunction with diet and increased excersice, Qsiva helps to lose weight and keep the weight down. It contains Phentermine and Topiramate as the active substances and it is given by mouth.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Qsiva, together with measures to minimise such risks and the proposed studies for learning more about Qsiva's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Qsiva, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Qsiva is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Qsiva are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Qsiva. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

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 events (PHEN)
Important missing information	Elderly > 70 years
	Patients at high cardiovascular risk

TPM: risk based on data for topiramate; PHEN: risk based on data for phentermine

II.B Summary of important risks

Important Identified Risk 1: Cognitive impairment	
Evidence for linking the risk to the medicine	Topiramate is associated with cognitive impairment at doses used to treat epilepsy. The most common cognitive effects seen in epileptic patients are sedation, somnolence, distractibility, memory impairment, insomnia, and dizziness. The frequency of adverse events in the Cognitive Disorders Class were higher than placebo for all dose levels of Qsiva and there was a dose-related increase in frequency.
Risk factors and risk groups	Rapid titration or high initial dose of Qsiva may, due to the TPM component, be associated with higher incidence of cognitive events such as attention, memory and language/word-finding impairments. Cognitive effects may impact on the patient's ability to drive or operate machinery.

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.7, 4.8; PL sections 2, 3, 4 Prescription only medicine Additional risk minimisation measures: Prescriber's guide and checklist and Patient guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: none
Important Identified Risk 2: Psychiatric disorders (depression/anxiety, including suicidal behaviour and ideation)	
Evidence for linking the risk to the medicine	Psychiatric disorders are well characterised side effects of treatment with TPM and PHEN. Psychiatric events have been reported with a dose dependent increase in reporting rates with increasing doses of Qsiva in clinical studies. Antiepileptic drugs, including topiramate, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. In clinical studies no increase in cases of suicidal ideation was observed for Qsiva treatment compared to placebo treatment. Suicidal behaviour was not reported. Cases of suicidal ideation and behaviour have been reported in the post-marketing setting for Qsiva-treated patients.
Risk factors and risk groups	An increasing BMI is associated with an increasing risk of suicidal ideation as well as greater feelings of perceived burdensomeness as compared to individuals with lower BMI. No specific risk groups or factors for developing other psychiatric disorders were identified in the Qsiva clinical study program
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8; PL sections 2, 4 Prescription only medicine Additional risk minimisation measures: Prescriber's guide and checklist and Patient guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Drug use PV study
Important Identified Risk 3: Teratogenicity	
Evidence for linking the risk to the medicine	Based largely on animal developmental toxicity studies, but also data from several human pregnancy registries there is approximately 3-fold increase in the incidence of orofacial clefts in infants born to women exposed to topiramate at antiepileptic doses.
Risk factors and risk groups	Women of childbearing potential not using effective forms of contraception or who are planning to become pregnant.

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.6; PL section 2 Prescription only medicine Additional risk minimisation measures: Prescriber's guide and checklist and Patient guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Pregnancy PV study
Important Identified Risk 4: Elevations in serum creatinine	
Evidence for linking the risk to the medicine	During the clinical development program of Qsiva, there was an observed increase in serum creatinine, which peaked at week 4 of study treatment, and in most patients was transient and returned towards baseline levels over time. However, there were a minority of subjects who continued to have persistent creatinine elevations during the clinical studies.
Risk factors and risk groups	No risk factors are identified. Largest increases in serum creatinine with exposure to Qsiva were observed in patients with high glomerular filtration rates, which relativises the risk.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8; PL section 4 Additional risk minimisation measures: none
Additional pharmacovigilance activities	Additional pharmacovigilance activities: none
Important Potential Risk 1: Serious cardiovascular events	
Evidence for linking the risk to the medicine	Phentermine possesses a stimulating sympathomimetic effects. There was a consistent trend for a small increase in mean heart rate throughout 1—year of treatment with PHEN/TPM 15/92 mg.
Risk factors and risk groups	No risk groups or factors have been identified. There is a theoretical risk in patients at high cardiovascular risk including those with a history of advanced cardiovascular disease. Prescribers should weigh the benefits and risks of use of Qsiva in these patients carefully.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.5, 4.8; PL sections 2, 4 Additional risk minimisation measures: Prescriber's guide and checklist and Patient guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Drug use PV study

Missing Information 1: Use in the Elderly (> 70 years)	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 Additional risk minimisation measures: none
Missing Information 2: Use in patients at high cardiovascular risk	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4; PL section 2 Additional risk minimisation measures: none

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of Qsiva.

II.C.2 Other studies in post-authorisation development plan

Two prospective observational studies are planned for Qsiva using national health registries.

1. Study OB-906: Pregnancy PV study
2. Study OB-907: Drug use PV study