Swiss Summary of the Risk Management Plan (RMP) for Dengue Tetravalent Vaccine (Live, Attenuated) (Qdenga)

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Marketing Authorization Holder: Takeda Pharma AG

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risk as well as to prevent or minimise them.

The RMP summary of QDenga is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of QDenga in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Takeda Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of QDenga.

Summary of risk management plan for QDenga (Dengue tetravalent vaccine (live, attenuated))

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

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

This summary of the RMP for Qdenga should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Qdenga is authorised for the prevention of dengue disease in individuals from 4 years of age (see SmPC for the full indication). It contains Dengue virus serotype 1 (live, attenuated), Dengue virus serotype 2 (live, attenuated), Dengue virus serotype 3 (live, attenuated) and Dengue virus serotype 4 (live, attenuated) as the active substances and it is given by subcutaneous injection.

Further information about the evaluation of Qdenga's benefits can be found in Qdenga's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/qdenga

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

Important risks of Qdenga, together with measures to minimise such risks and the proposed studies for learning more about Qdenga'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 package leaflet 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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 Qdenga is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Qdenga are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Qdenga. 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 (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Anaphylaxis including anaphylactic shock • Dengue disease due to waning protection against dengue over time • Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus
Missing information	• Safety profile of inadvertent use in pregnant or lactating women • Safety and immunogenicity in immunocompromised individuals • Safety and immunogenicity of concomitant administration with other vaccines other than HAV and YF • Safety and reactogenicity of a booster dose

II.B Summary of important risks

Important Potential Risk: Anaphylaxis including anaphylactic shock	
Evidence for linking the risk to the medicine	There were no TDV-related anaphylactic reactions or anaphylactic shock events reported during the clinical development program. Anaphylaxis is a rare, severe allergic reaction and can occur with vaccines.
Risk factors and risk groups	Clinical risk factors that have been identified for anaphylaxis are: - History of allergies to the active substances or any of the other components of the Dengue Tetravalent Vaccine (Live, Attenuated) Takeda referred to as TDV vaccine,

	- History of an allergic reaction after a previous immunisation with TDV, - Coexisting atopic disease, particularly asthma. However, allergic reactions may occur in patients without known risk factors.
Risk minimization measures	Routine risk minimisation measures: - Summary of product characteristics (SmPC) Section 4.3 and Section 4.4 - Package Leaflet (PL) Section 2 No additional risk minimisation measures

Important Potential Risk: Dengue disease due to waning protection against dengue over time	
Evidence for linking the risk to the medicine	In a year-by-year analysis until 4.5 years after the second dose in Trial DEN-301, VE in preventing VCD was shown for all four serotypes in baseline dengue seropositive subjects. In baseline seronegative subjects, VE was shown for DENV-1 and DENV-2, but not suggested for DENV-3 and could not be shown robustly for DENV-4 due to lower incidence of cases. During the third year of Trial DEN-301, although some decline in efficacy compared with Year 2 was observed, largely driven by non-hospitalized VCD cases, efficacy against VCD was demonstrated overall, as well as in both baseline seronegative and seropositive subjects. Efficacy against VCD leading to hospitalization remained robust with little change compared with Year 2. The data obtained in the last 18 months of follow-up up to Month 54 showed continued long-term protection against overall VCD and a sustained high level of protection against hospitalized VCD regardless of baseline serostatus. Waning immunity resulting in a loss of protection over time is applicable to all vaccines. The maximum duration of protection with TDV is not known currently.
Risk factors and risk groups	In general, lack of response to vaccination can occur due to immunodeficiency, elderly age, interference due to wild type infectious agents, acute or chronic disease and suboptimal health, as well as nutritional status, immunological interference. In addition, there may be failure to respond due to the normal expected variation in immune response across healthy individuals (i.e., a "low responder" or "non-responder"). Additionally, vaccine effectiveness may wane with increasing time since vaccination. Depending on the vaccine, rates of decline of vaccine effectiveness may vary across antigens. A number of variables influence duration of vaccine protection, including age, serostatus at vaccination, presence or absence of exposures to circulating wild type virus (natural boosting),

	possible evolution of the wild type virus, as well as unknown factors. No risk factors have been identified for TDV vaccination failure.
Risk minimization measures	Routine risk minimisation measures: - SmPC Section 4.4 - PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose) DEN-303 – Long-term immunogenicity trial (includes administration of a booster dose) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Severe and/or hospitalized dengue following vaccination caused by dengue virus serotype 3 or 4 in individuals not previously infected by dengue virus	
Evidence for linking the risk to the medicine	Efficacy results by baseline dengue serostatus (determined for all subjects), demonstrated overall VE against VCD and VCD leading to hospitalization regardless of prior exposure to dengue. Efficacy against individual dengue serotypes varied. The totality of data on VCD, hospitalized VCD, and severe forms of dengue, along with the clinical characteristics of these cases, as assessed in Trials DEN-301, DEN-313, and DEN-204, did not reveal an identified risk of increased disease severity or disease enhancement attributable to vaccination in the post-vaccination period. Exploratory efficacy analyses at 54 months after the second vaccine dose did not suggest efficacy for VCD caused by serotype DENV-3 in baseline seronegative subjects (RR: 1.11 [95% CI: 0.62, 1.99]). For hospitalized VCD caused by DENV-3 there were with 11 cases in the TDV group (0.3%) compared with 3 cases in placebo group (0.2%), with a relative risk of 1.81 (95% CI: 0.51, 6.48). In the baseline seronegative subgroup, a total of 2 subjects with VCD were assessed as severe dengue as defined by the Adjudication Committee (both in the TDV group; 0.05% of 3714 subjects). Both cases occurred early in the trial during Parts 1 and 2 (i.e., before 18 months post second dose). Five subjects experienced DHF as per programmed algorithm, WHO 1997 DHF criteria), 4 of 3714 subjects (0.11%) in the TDV group and 1 of 1832 subjects (0.05%) in the placebo group. Of note, 1 of these 4 DHF cases in the TDV group was also classified as DCAC-defined severe dengue. All of these cases in baseline

	seronegative subjects were caused by DENV-3. The assessment of whether TDV may be associated with an increased risk of severe forms of dengue in baseline seronegative subjects who experience VCD caused by serotype DENV-3 remained inconclusive; the data are limited by the small number of cases. In baseline seronegative subjects, an increased risk of hospitalization and/or clinically severe forms of dengue caused by serotype DENV-3 following vaccination in subjects not previously infected by dengue virus is considered an important potential safety risk. Conservatively, due to limited data for DENV-4, risk of hospitalization due to dengue and/or clinically severe forms of dengue caused by serotype DENV-4 in baseline seronegative subjects is considered an important potential safety risk, although up the 54 months after the second vaccine dose no hospitalisations caused by DENV-4 occurred in TDV recipients.
Risk factors and risk groups	No risk factors for severe dengue with TDV have been identified.
Risk minimization measures	Routine risk minimisation measures: - SmPC Section 4.4 - PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose). DEN-303 – Long-term immunogenicity trial (includes administration of a booster dose) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Safety profile of inadvertent use in pregnant or lactating women	
Risk minimization measures	Routine risk minimisation measures: - SmPC Section 4.3, Section 4.4 and Section 4.6 - PL Section 2 No additional risk minimisation measures

Missing Information: Safety and immunogenicity in immunocompromised individuals	
Risk minimization measures	Routine risk minimisation measures: - SmPC Section 4.3 and Section 4.5 - PL Section 2 No additional risk minimisation measures

Missing Information: Safety and immunogenicity of concomitant administration with other vaccines other than HAV and YF	
Risk minimization measures	Routine risk minimisation measures: - SmPC Section 4.5 - PL Section 2 No additional risk minimisation measures
Additional pharmacovigilance activities	Coadministration with 9vHPV vaccine Trial (DEN-308) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Safety and reactogenicity of a booster dose	
Risk minimization measures	Routine risk minimisation measures: - SmPC Section 4.2 No additional risk minimisation measures
Additional pharmacovigilance activities	Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (includes administration of a booster dose) DEN-303 – Long-term immunogenicity trial (includes administration of a booster dose) See Section II.C of this summary for an overview of the post-authorisation development plan.

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 Qdenga.

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

Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (Part 4 and 5)

Purpose of the study:

WHO recommends long-term follow-up to evaluate the safety of dengue vaccines for 3 to 5 years. The total follow-up period including Parts 1, 2 and 3 of this study last 4 to 4.5 years after the second dose. For those participants in the booster phase, parts 4 and 5, there is approximately 2 years of additional follow-up.

Long-term safety and antibody persistence of TDV and the impact of a booster dose (study DEN-303)

Purpose of the study:

This Phase 3 trial will evaluate long-term antibody persistence and safety data in healthy subjects in areas non-endemic for dengue who have previously received a primary TDV vaccination in either DEN-304 and DEN-315 trials (termed here as "parent trials"). It will then go on to assess the immunogenicity and safety of a TDV booster dose in this population.

Immunogenicity and safety of TDV and 9vHPV in subjects aged ≥9 to <15 years (study DEN-308)

Purpose of the study:

The WHO recommends that new vaccines should be introduced according to existing national immunisation programs. Recombinant 9-valent human papillomavirus (HPV) vaccine is recommended either in a 2-dose or 3-dose schedule 6 to 12 months apart in subjects 9 through 14 years of age. Further, if the second dose is administered earlier than 5 months after the first dose, then a third dose should be administered at least 4 months after the second dose. Many similarities exist between the proposed vaccination schedule for TDV and the approved schedule for 9-valent HPV (9vHPV) vaccine, including the overlapping target age group and the potential delivery through school immunisation programs.

In order to avoid barriers to the inclusion of TDV in routine national vaccination programs, the effect of adding TDV to such programs needs to be examined. This is particularly relevant for low-income countries where the cost of a standalone vaccination could be too high, and potentially undermine TDV uptake, if inclusion in routine vaccine schedules were not possible.