Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Qdenga powder and solvent for solution for injection

Qdenga powder and solvent for solution for injection in pre-filled syringe

Dengue virus serotype 1 (live, attenuated)*: ≥ 3.3 log10 PFU/dose**
Dengue virus serotype 2 (live, attenuated)#: ≥ 2.7 log10 PFU/dose**
Dengue virus serotype 3 (live, attenuated)*: ≥ 4.0 log10 PFU/dose**
Dengue virus serotype 4 (live, attenuated)*: ≥ 4.5 log10 PFU/dose**

PLGB 16189/0125-0126

Takeda UK Limited

LAY SUMMARY

Qdenga powder and solvent for solution for injection
Dengue tetravalent vaccine (live, attenuated)

This is a summary of the Public Assessment Report (PAR) for Qdenga. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Qdenga in this lay summary for ease of reading.

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 5 December 2022 (EMEA/H/C/005155/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

These applications were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

For practical information about using Qdenga, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Qdenga how does it work, and what is it used for?
Qdenga is a vaccine. It is used to help protect people against dengue. Dengue is a disease caused by dengue virus serotypes 1, 2, 3 and 4.

Qdenga contains weakened versions of these 4 dengue virus serotypes so it cannot cause dengue disease.

Qdenga is given to adults, young people and children (from 4 years of age). Qdenga should be used according to official recommendations.

Qdenga stimulates the body's natural defences (immune system). This helps to protect against the viruses that cause dengue if the body is exposed to these viruses in the future.

Dengue is caused by a virus.

- The virus is spread by mosquitos (Aedes mosquitos).
- If a mosquito bites someone with dengue it can pass the virus on to the next people it bites.

Dengue is not passed directly from person to person.

Signs of dengue include fever, headache, pain behind the eyes, muscle and joint pain, feeling or being sick (nausea and vomiting), swollen glands or skin rash. Signs of dengue usually last for 2 to 7 days. The patient can also be infected with dengue virus but show no signs of illness. Occasionally dengue can be severe enough for the patient to have to go to hospital and in rare cases it can cause death. Severe dengue can give a high fever and any of the following: severe abdominal (belly) pain, persistent sickness (vomiting), rapid breathing, severe bleeding,

bleeding in the stomach, bleeding gums, feeling tired, feeling restless, coma, having fits (seizures) and organ failure.

How are Qdenga used?
The pharmaceutical form of these medicines is a powder and solvent for solution for injection and the route of administration is subcutaneous use.

Qdenga is given by your doctor or nurse as an injection under the skin (via subcutaneous injection) in the upper arm. It must not be injected into a blood vessel.

The person will receive 2 injections. The second injection is given 3 months after the first injection.

There are no data in adults above 60 years of age. The doctor can provide advice on whether it is beneficial for a person to receive Qdenga. Qdenga should be used according to official recommendations.

Instructions for preparing the vaccine intended for medical and healthcare professionals are included in the leaflet available on the MHRA products website.

What to do if a scheduled injection of Qdenga is missed?
- The doctor will decide when to give the missed injection. It is important that you or your child follow the instructions of your doctor, pharmacist or nurse about the follow-up injection.
- If you forget or are not able to go back at the scheduled time, ask your doctor, pharmacist or nurse for advice.

For further information on how Qdenga are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Qdenga have been shown in studies?
This vaccine was shown to be effective at preventing fever due to dengue disease in children and adolescents in the 12 months following the second injection. In a main study in 8 countries in Latin America and the Asia Pacific region, about 20,000 children between the age of 4 to 16 years were given Qdenga or placebo (a dummy injection). The study showed a reduction by 80% in the number of fever cases caused by confirmed dengue disease in those who received the vaccine (61 cases in 12,700 children) compared with those given placebo (149 cases in 6,316 children).

The vaccine also reduced hospitalisation due to dengue by 90%. In the 18 months after receiving the second injection, 0.1% (13 out of 12,700) of children given the vaccine were hospitalised because of confirmed dengue, compared with 1.0% (66 out of 6,316) of children given placebo.

What are the possible side effects of Qdenga?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why were Qdenga approved?
MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use. Qdenga has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. See section VIII of this report (overall conclusion, benefit/risk and recommendation).

What measures are being taken to ensure the safe and effective use of Qdenga?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Qdenga The RMP details the important risks of Qdenga, how these risks can be minimised, any uncertainties about Qdenga (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Qdenga:

Summary of safety concerns	
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

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Qdenga are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Qdenga

Marketing authorisations were granted in Great Britain on 26 January 2023.

The full PAR for Qdenga follows this summary.

This summary was last updated in May 2023.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Qdenga powder and solvent for solution for injection and Qdenga powder and solvent for solution for injection pre-filled syringe (PLGB 16189/0125-0126) could be approved.

The products are approved for the following indications:
The prevention of dengue disease in individuals from 4 years of age. The use of Qdenga should be in accordance with official recommendations.

Qdenga contains live attenuated dengue viruses. The primary mechanism of action of Qdenga is to replicate locally and elicit humoral and cellular immune responses against the four dengue virus serotypes.

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 5 December 2022 (EMEA/H/C/005155/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).
For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

These applications were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

At the time of submission of the application, the PIP P/0429/2020 was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations were granted on 26 January 2023.

II. PRODUCT INFORMATION

Summaries of Product Characteristics (SmPCs)

The SmPCs are in line with current guidelines and were satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for these applications is satisfactory.

The grant of marketing authorisations was recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations was recommended.

V. CLINICAL ASPECTS

MHRA considered that the clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance measures have been proposed, and these are acceptable.

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 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 Dengue Tetravalent Vaccine (live, Attenuated) referred to as TDV. – 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 minimisation 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 minimisation 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 due to dengue and/or clinically severe forms of dengue caused by serotype DENV-3 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 minimisation 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 minimisation 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 minimisation 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 minimisation 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 minimisation 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 Summary of on-going and planned additional pharmacovigilance measures

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Efficacy, Safety and Immunogenicity of TDV in Trial DEN-301 (Part 4 and 5) Study status: ongoing	To evaluate the efficacy, immunogenicity and safety of a TDV booster dose	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 Safety and reactogenicity of a booster dose	Interim report: End Part 4 CSR	Q4 2024 (planned)
			Final Report (Final CSR Parts 1, 2, 3, 4 and 5)	Q1 2026 (planned)
Long-term safety and antibody persistence of TDV and the impact of a booster dose (Trial DEN-303) Study status: ongoing	To assess the immunogenicity and safety of a TDV booster dose in Healthy Adolescents and Adults.	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 Safety and reactoge-nicity of a booster dose	Final CSR	Q1 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Immunogenicity and safety of TDV and 9vHPV in subjects aged ≥9 to <15 years (Trial DEN-308) Study status: ongoing	To investigate the immunogenicity and safety of the co-administration of a subcutaneous dengue tetravalent vaccine and intramuscular recombinant 9-valent human papillomavirus (9vHPV) vaccine in subjects aged ≥9 to <15 years in endemic country for dengue	Safety and immunogenicity of concomitant administration with other vaccines other than HAV and YF	Final CSR	Q4 2023

Note: Trial DEN-401 was migrated from RMP to the list of post-authorisation measures

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

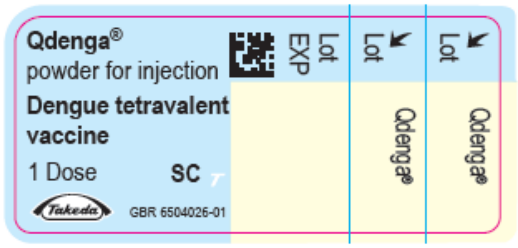
The quality of the products is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of these products in the prevention of dengue disease in individuals from 4 years of age.

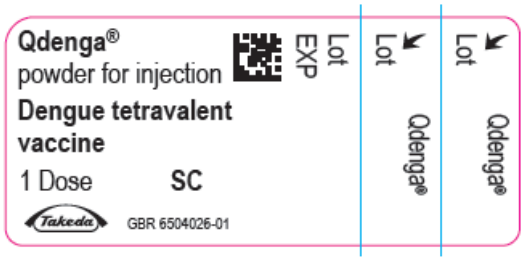
Qdenga has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk.

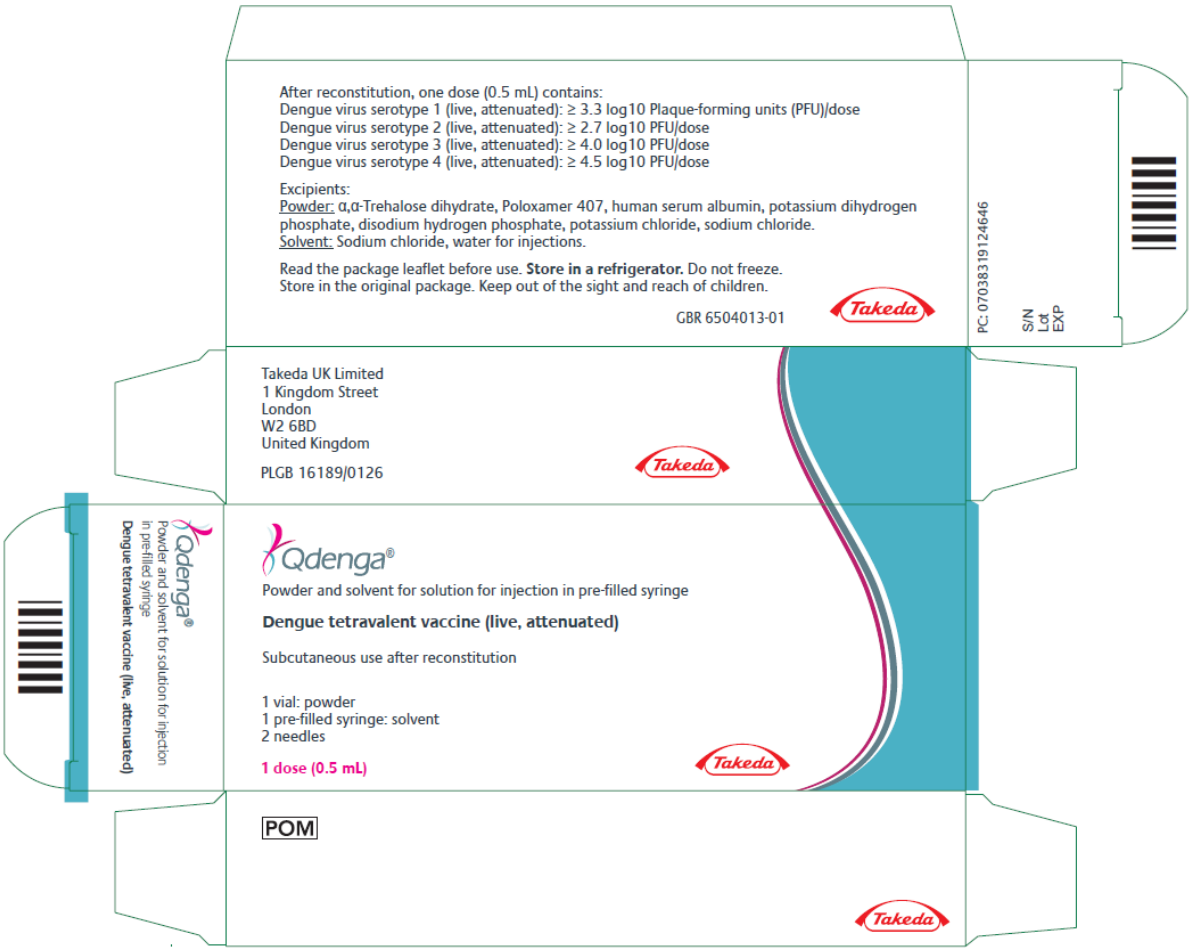
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved Great Britain versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.

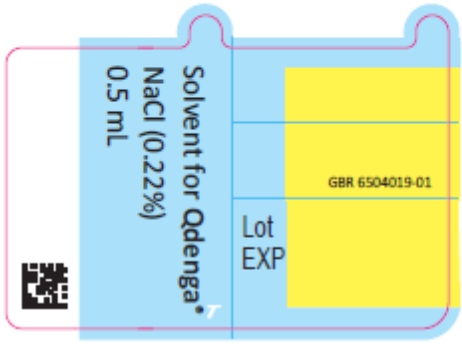

Qdenga®
powder for injection
Dengue tetravalent vaccine
1 Dose
SC
GBR 6504026-01
Lot
EXP
Lot
Qdenga®
Lot
Qdenga®


Qdenga®
powder for injection
Dengue tetravalent vaccine
1 Dose
SC
GBR 6504026-01
Lot
EXP
Lot
Qdenga®
Lot
Qdenga®


After reconstitution, one dose (0.5 mL) contains:
Dengue virus serotype 1 (live, attenuated): ≥ 3.3 log10 Plaque-forming units (PFU)/dose
Dengue virus serotype 2 (live, attenuated): ≥ 2.7 log10 PFU/dose
Dengue virus serotype 3 (live, attenuated): ≥ 4.0 log10 PFU/dose
Dengue virus serotype 4 (live, attenuated): ≥ 4.5 log10 PFU/dose
Excipients:
Powder: α,α-Trehalose dihydrate, Poloxamer 407, human serum albumin, potassium dihydrogen phosphate, disodium hydrogen phosphate, potassium chloride, sodium chloride.
Solvent: Sodium chloride, water for injections.
Read the package leaflet before use. Store in a refrigerator. Do not freeze.
Store in the original package. Keep out of the sight and reach of children.
GBR 6504013-01
PC: 07038319124646
S/N
Lot
EXP
Takeda UK Limited
1 Kingdom Street
London
W2 6BD
United Kingdom
PLGB 16189/0126
Qdenga®
Powder and solvent for solution for injection in pre-filled syringe
Dengue tetravalent vaccine (live, attenuated)
Subcutaneous use after reconstitution
1 vial: powder
1 pre-filled syringe: solvent
2 needles
1 dose (0.5 mL)
POM
Qdenga®
Powder and solvent for solution for injection in pre-filled syringe
Dengue tetravalent vaccine (live, attenuated)

Syringe label

Top label



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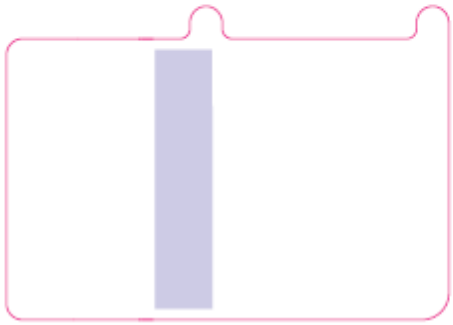
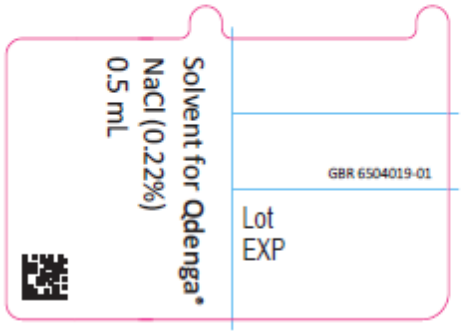


Top label text only



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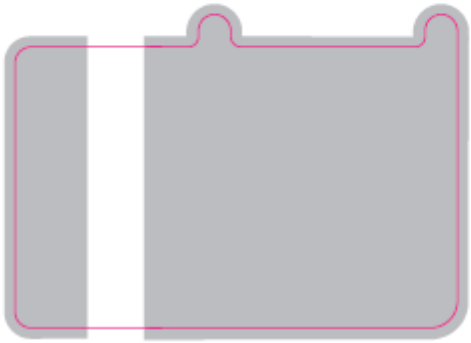

IX. TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**