GARDASIL 9 DOSSIER

Table of contents of Marketing Authorisation Application dossier (as submitted in EURS)

Module 1

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

13. Written consent(s) of the competent authorities regarding GMO release in the environment.

14. Scientific Advice given by CHMP and/or by member state(s)

15. Copy of Marketing Authorization(s) required under Article 8(j)-(L) of Directive 2001/83/EC in the EEA and the equivalent in third countries on request (a photocopy of the pages which give the marketing authorization number, the date of authorisation and the page which has been signed by the authorizing competent authority will suffice).

16. Correspondence with the European Commission regarding multiple applications

17. List of Mock-ups or Samples/specimens sent with the application, as appropriate (see Notice to Applicants, volume 2A, chapter 7)

18. Copy of the Orphan Designation Decision

19. List of proposed (invented) names and marketing authorisation holders in the concerned member states

20. Copy of EMEA certificate for a Vaccine Antigen Master File (VAMF).

21. Copy of EMEA certificate for a Plasma Master File (PMF)

22. For each active substance, attach a Statement(s) from the Qualified Person of the manufacturing authorisation holder in Section 2.5.1 and from the Qualified Person of each of the manufacturing authorisation holders (i.e. located in EEA) listed in Section 2.5.2 where the active substance is used as a starting material that the active substance is manufactured in compliance with the detailed guidelines on good manufacturing practice for starting materials. Alternatively, such Statement may be signed by one Qualified Person on behalf of all QPs involved (provided this is clearly indicated)

1.3 Product Information

1.3.1 SPC, Labelling and Package Leaflet (publicly available in the SMPc)

1.3.2 Mock-up

1.3.3 Specimen

1.3.4 Consultation with Target Patient Groups

1.3.5 Product Information already approved in the Member States

1.3.6 Braille

1.4 Information about the Experts (**MOST LIKELY NOT RELEASABLE AS IT CONTAINS THE CVs OF THE EXPERTS WHICH ARE CONSIDERED PPD)**

1.4.1 Quality

1.4.2 Non-Clinical

1.4.3 Clinical

1.5 Specific Requirements for Different Types of Applications

1.5.1 Information for Bibliographical Applications

1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications

1.5.3 (Extended) Data / Market Exclusivity

1.5.4 Exceptional Circumstances

1.5.5 Conditional Marketing Authorisation

1.6 Environmental Risk Assessment

1.6.1 Non-GMO

1.6.2 GMO

1.7 Information relating to Orphan Market Exclusivity

1.7.1 Similarity

1.7.2 Market Exclusivity

1.8 Information relating to Pharmacovigilance

1.8.1 Pharmacovigilance System

1.8.2 Risk-management System

1.9 Information relating to Clinical Trials

1.10 Information relating to Paediatrics

Responses to Questions

Additional Data

Module 2 Common Technical Document Summaries

2.1 CTD Table of Contents (Module 2 – 5)

2.2 Introduction

2.3 Quality Overall Summary – Introduction COMMERCIAL CONFIDENTIAL INFORMATION NON - RELEASABLE

2.3.S Quality Overall Summary – Drug Substance

2.3.S.1 General Information (name, manufacturer)

2.3.S.2 Manufacture (name, manufacturer)

2.3.S.3 Characterisation (name, manufacturer)

2.3.S.4 Control of Drug Substance (name, manufacturer)

2.3.S.5 Reference Standards or Materials (name, manufacturer)

2.3.S.6 Container Closure System (name, manufacturer)

2.3.S.7 Stability (name, manufacturer)

2.3.P Quality Overall Summary – Drug Product

- 2.3.P.1 Description and Composition of the Drug Product (name, dosage form)
- 2.3.P.2 Pharmaceutical Development (name, dosage form)
- 2.3.P.3 Manufacture (name, dosage form)
- 2.3.P.4 Control of Excipients (name, dosage form)
- 2.3.P.5 Control of Drug Product (name, dosage form)
- 2.3.P.6 Reference Standards or Materials (name, dosage form)
- 2.3.P.7 Container Closure System (name, dosage form)
- 2.3.P.8 Stability (name, dosage form)

2.3.A Quality Overall Summary – Appendices

- 2.3.A.1 Facilities and Equipment (name, manufacturer)
- 2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)
- 2.3.A.3 Excipients

2.3.R Quality Overall Summary – Regional Information

2.4 Nonclinical Overview

2.5 Clinical Overview

2.6 Nonclinical Written and Tabulated Summaries

- 2.6.1 Introduction
- 2.6.2 Pharmacology Written Summary
- 2.6.3 Pharmacology Tabulated Summary
- 2.6.4 Pharmacokinetics Written Summary
- 2.6.5 Pharmacokinetics Tabulated Summary
- 2.6.6 Toxicology Written Summary
- 2.6.7 Toxicology Tabulated Summary

2.7 Clinical Summaries

- 2.7.1 Summary of Biopharmaceutic and Associated Analytical Methods
- 2.7.2 Summary of Clinical Pharmacology Studies
- 2.7.3 Summary of Clinical Efficacy
- 2.7.4 Summary of Safety
- 2.7.5 References
- 2.7.6 Synopses of Individual Studies

Module 3 Quality (NON RELEASABLE COMMERCIAL CONFIDENTIAL INFORMATION)

3.2.P.3.1 Manufacturer(s)

3.2.P.3.2 Batch formula

3.2.P.3.3 Description of Manufacturing Process and Process Controls

3.2.P.3.4 Controls of critical steps and intermediates

3.2.P.3.5 Process validation and / or evaluation

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

3.2.P.4.2 Analytical procedures

3.2.P.4.3 Validation of analytical procedures

3.2.P.4.4 Justification of specifications

3.2.P.4.5 Excipients of human or animal origin

3.2.P.4.6 Novel Excipients (ref to A 3)

3.2.P.5 Control of drug product

3.2.P.5.1 Specification(s)

3.2.P.5.2 Analytical Procedures

3.2.P.5.3 Validation of Analytical Procedures

3.2.P.5.4 Batch analyses

3.2.P.5.5 Characterisation of Impurities

3.2.P.5.6 Justification of specification(s)

3.2.P.6 Reference Standards or Materials

3.2.P.7 Container Closure System

3.2.P.8 Stability

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION

3.3 Literature References

Module 4 Nonclinical Study Reports

4.1 Module 4 Table of Contents

4.2 Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

4.2.1.2 Secondary Pharmacodynamics

4.2.1.3 Safety Pharmacology

4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)

4.2.2.2 Absorption

4.2.2.3 Distribution

4.2.2.4 Metabolism

4.2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)

4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity (in order by species, by route)

4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)

4.2.3.3 Genotoxicity

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

4.2.3.4.1 Long-term studies (in order by species; including rangefinding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeatdose toxicity or pharmacokinetics)

4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other

4.3 Literature References

Module 5 Clinical Study Reports

5.1 Module 5 Table of Contents

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

5.3.1.3 *In vitro-In vivo* Correlation Study Reports

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

5.3.5 Reports of Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

5.3.5.3 Reports of Analyses of Data from More Than One Study

5.3.5.4 Other Clinical Study Reports

5.3.6 Reports of Post-Marketing Experience

5.3.7 Case Report Forms and Individual Patient Listings

5.4 Literature References