Impact of EU label changes for medicinal products containing methotrexate for weekly administration: risk awareness and adherence, A survey study

SC02 EMA/2018/19/PE

Protocol

21 February 2022

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Protocol Approval and Sign-off

I confirm that I have read the contents of this protocol and its attachments. I approve the protocol in its current form.

IQVIA Principal	Massoud Toussi	DocuSigned by Massoud Toussi Massoud Toussi | J'approuve ce document mars 1, 2022 | 7:31:31 PM JST 0BB375BD90E341C7B8519B0BD291BDC5	mars 1, 2022
	Print name, title here	Signature	Date
Lead Epidemiologist	Leila Karimi	DocuSigned by Leila Karimi Leila Karimi | I approve this document March 1, 2022 | 7:14:06 AM PST 9C6284A28E114BCFB5848DEF9C4D5C9B	March 1, 2022
		Signature	Date
Author **(*if different from the Epidemiologist*)**	Print name, title here	Signature	Date
For PASS Studies only **Principal Investigator**	Massoud Toussi	DocuSigned by Massoud Toussi Massoud Toussi | J'approuve ce document mars 1, 2022 | 7:31:58 PM JST 0BB375BD90E341C7B8519B0BD291BDC5	mars 1, 2022
	Print name, title here	Signature	Date

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

PASS INFORMATION

TITLE	Impact of EU label changes for medicinal products containing methotrexate for weekly administration: risk awareness and adherence, A survey study
PROTOCOL VERSION IDENTIFIER	2.0
DATE OF LAST VERSION OF PROTOCOL	NA
EU PAS REGISTER NUMBER	EUPAS44827
ACTIVE SUBSTANCE	Methotrexate
MEDICINAL PRODUCT(S)	Methotrexate
PRODUCT REFERENCE	NA
PROCEDURE NUMBER	SC02 EMA/2018/19/PE
MARKETING AUTHORISATION HOLDER(S) (MAH)	Multiple
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES	The aim of the current study is to examine the effectiveness of product-specific risk-minimisation measures (RMMs) for methotrexate (MTX), by carrying out a survey to evaluate the impact of European union (EU) label changes for medicinal products containing MTX for weekly administration, with reference to the 2019 EMA referral procedure (EMEA/H/A-31/1463). The primary objectives of the study are: 1. To determine the extent of prescriber awareness and knowledge of the risk of inadvertent overdose due to daily instead of weekly use and adherence to summary of product

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	characteristics (SmPC) recommendations for oral and parenteral MTX-containing medicines with at least one indication requiring once-weekly dosing, with particular focus on the following elements: 1.1. Receipt and awareness of the direct healthcare professional communication (DHPC) 1.2. Knowledge of the dosing frequency of MTX in the treatment of inflammatory diseases (e.g. rheumatologic/dermatological diseases or Crohn's disease), by indication 1.3. Knowledge of the updated posology instructions and boxed warning 1.4. Receipt and awareness of the new or updated educational materials for healthcare professionals (HCPs) (checklist or guide) and awareness of the patient card to avoid the risk of inadvertent overdose due to daily instead of weekly use 2. To determine the extent of pharmacist awareness and knowledge of the patient card, the visual reminder on the outer packaging and the need to mark the day of intake for indications requiring once-weekly dosing regimens, and adherence to marking the day of intake on the outer packaging for indications requiring once-weekly dosing regimens 3. To determine the extent of patient awareness and knowledge of the following elements introduced to avoid incorrect administration schedules for oral and parenteral MTX-containing medicines with at least one indication requiring once-weekly dosing: 3.1. Receipt and awareness of the patient card, and knowledge of symptoms of MTX overdose and the purpose of the patient card (i.e. to note the day of intake for indications requiring once-weekly dosing regimens, and steps to be taken if symptoms arise, and to alert any HCP not familiar with MTX treatment about the once-weekly dosing regimen e.g. on hospital admission, change of care etc.) 3.2. Knowledge of the once-weekly dosing frequency of MTX in the treatment of inflammatory diseases (e.g. rheumatologic/dermatological diseases or Crohn's disease), for his/her indication 3.3. a) Awareness and knowledge of the visual reminder on the packaging of oral and parenteral MTX-containing products; b) Awareness and knowledge of the boxed warning in the package leaflet.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

COUNTRY(-IES) OF STUDY	France, Germany, Greece, Poland, and Sweden
AUTHORS	Leila Karimi and Shubhra Singh, IQVIA Supervised by Massoud Toussi, IQVIA

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Marketing authorisation holder(s)

Marketing authorisation holder(s)	NA
MAH Contact Person	NA

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

1. TABLE OF CONTENTS

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

2. LIST OF ABBREVIATIONS

AE	adverse event
CI	confidence interval
DHPC	Direct Healthcare Professional Communication
EC	European Commission
EDC	electronic data capture
EM	educational material
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EphMRA	European Pharmaceutical Marketing Research Association
EU	European Union
FDA	Food and Drug Administration
GVP	good pharmacovigilance practice
HCP	healthcare professional
ISO	International Standards Organisation
MTX	methotrexate
PASS	post-authorisation safety study
RMM	risk-minimisation measure
SAP	statistical analysis plan
SOP	standard operating procedure
SmPC	summary of product characteristics

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

3. RESPONSIBLE PARTIES

Sponsor:

European Medicines Agency

CRO:

IQVIA Inc.

One IMS Drive

Plymouth Meeting, PA 19462

Project team:

Dr. Massoud Toussi, Principal Investigator, Senior Principal, Pharmacoepidemiology and Drug Safety, IQVIA RWES, France

Leila Karimi, Lead Epidemiologist, Engagement Manager, Pharmacoepidemiology and Drug Safety, IQVIA RWES, The Netherlands

Irina Panina, Project Manager, Associate Regulatory Affairs Director, IQVIA Global Database Studies, Estonia

Johanna Käll Bernards, Primary Intelligence Project Manager, Consultant, IQVIA Primary Intelligence, Sweden

Mo Wang, Lead Statistician, Statistical Programmer, IQVIA Global Database Studies, Sweden

Shubhra Singh, Medical Writer, Senior Consultant, India

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

4. ABSTRACT

Full Study Title: Impact of EU label changes for medicinal products containing methotrexate for weekly administration: risk awareness and adherence, A survey study

Protocol version 2.0 dated 21 February 2022

Protocol supervisor: Dr Massoud Toussi, Senior Principal, Pharmacoepidemiology, IQVIA, RWES

Email address: mtoussi@fr.imshealth.com

Rationale and background:

Methotrexate (MTX) is a synthetic organic compound belonging to a group of folate inhibitors used in treating low grade (acute) leukaemia in children. It has a pleotropic mechanism of action and is now widely used as a chemotherapeutic, immunosuppressant, anti-metabolite and anti-neoplastic agent in medical conditions like cancer, psoriasis, rheumatoid arthritis, Crohn's disease, multiple sclerosis, polyarticular juvenile idiopathic arthritis etc.

In 2019, a referral procedure (EMEA/H/A-31/1463) under Article 31 of Directive 2001/83/ European Commission (EC) based on pharmacovigilance data concluded that further risk-minimisation measures were required for oral and parenteral MTX-containing products that avoid incorrect administration schedules, i.e. inadvertent MTX overdose due to daily instead of weekly use. The review was based on post-marketing spontaneous case reports from EudraVigilance, including analysis of the root causes of medication errors, a stakeholder consultation and literature review. As a result of these data, measures were introduced for all oral and parenteral MTX formulations with at least one indication requiring once-weekly dosing (e.g. rheumatologic/dermatological diseases or Crohn's disease). This was achieved by updating section 4.2 of the summary of product characteristics (SmPC), putting visual reminders on the packaging of the product, switching from bottle to blister packaging, using a patient card with information on once-weekly dosing regimen and updating of existing educational materials (EMs) for healthcare professionals (HCPs) and direct healthcare professional communication (DHPC).

Research question and objectives:

The overall objective of the study is to evaluate the impact of these actions taken for MTX-containing medicinal products following the 2019 referral procedure. Study objectives are summarised as:

1. Determining the extent of prescriber awareness and knowledge of the risk of inadvertent overdose due to daily instead of weekly use and adherence to SmPC recommendations for oral and parenteral MTX-containing medicines with at least one indication requiring once-weekly dosing, with particular focus on the elements:

    1.1 Receipt and awareness of the DHPC

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

1.2 Knowledge of the dosing frequency of MTX in the treatment of inflammatory diseases (e.g. rheumatologic/dermatological diseases or Crohn's disease), by indication

1.3 Knowledge of the updated posology instructions and boxed warning

1.4 Receipt and awareness of the new or updated EMs for HCPs (checklist or guide) and awareness of the patient card to avoid the risk of inadvertent overdose due to daily instead of weekly use

2. Determining the extent of pharmacist awareness and knowledge of the patient card, the visual reminder on the outer packaging and the need to mark the day of intake for indications requiring once-weekly dosing regimens, and adherence to marking the day of intake on the outer packaging for indications requiring once-weekly dosing regimens

3. Determining the extent of patient awareness and knowledge of the following elements introduced to avoid incorrect administration schedules for oral and parenteral MTX-containing medicines with at least one indication requiring once-weekly dosing:

3.1 Receipt and awareness of the patient card, and knowledge of symptoms of MTX overdose and the purpose of the patient card (i.e. to note the day of intake for indications requiring once-weekly dosing regimens, and steps to be taken if symptoms arise, and to alert any HCP not familiar with MTX treatment about the once-weekly dosing regimen e.g. on hospital admission, change of care etc.)

3.2 Knowledge of the once-weekly dosing frequency of MTX in the treatment of inflammatory diseases (e.g. rheumatologic/dermatological diseases or Crohn's disease), for his/her indication

3.3 a) Awareness and knowledge of the visual reminder on the packaging of oral and parenteral MTX-containing products; b) Awareness and knowledge of the boxed warning in the package leaflet.

Study design: The survey will be a cross-sectional, multinational, and multichannel survey conducted among prescribers, pharmacists and patients in 5 European countries, France, Greece, Germany, Poland, and Sweden.

Population:

The following criteria will be checked at the beginning of the web questionnaire:

Inclusion criteria

- *For prescriber questionnaire*: Prescribers who have prescribed MTX in a single low dose once a week for indications that require weekly dosing in the past 3 months

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- *For pharmacist questionnaire*: Pharmacists who have dispensed MTX in a single low dose once a week for indications that require weekly dosing in the past 3 months
- *For patient questionnaire*: Patients who have been treated with a single low dose once a week for indications that require weekly dosing in the past 3 months

Exclusion criteria

Prescribers, pharmacists, and patients who declare having a conflict of interest with the survey (i.e. participants employed by regulatory bodies, pharmaceutical industries) or who do not provide consent for participating in the survey.

Variables*:*

Variables collected through the prescribers' survey:

- Variables related to prescribers' practice information (demographic information [country], gender [if available], primary specialty, duration of practice in primary specialty [inclusive of specialty trainings], practice setting [office or hospital-based or both], experience with MTX in the once-weekly indications [number of patients treated with MTX])
- Variables related to the prescriber's receipt and awareness of the DHPC and EMs (receipt and awareness of the DHPC, and of the new or updated EMs for HCPs [checklist or guide], awareness of the patient card)
- Variables related to the knowledge of the risks of inadvertent overdose due to daily instead of weekly use (knowledge of the dosing frequency of MTX in the treatment of inflammatory diseases [e.g. rheumatologic/dermatological diseases or Crohn's disease], knowledge of the updated posology instructions and boxed warning)
- Variables related to adherence to SmPC recommendations for oral and parenteral MTX-containing medicines with at least one indication requiring once-weekly dosing

Variables collected through the pharmacist survey:

- Variables related to pharmacists' practice information (demographic information [country], gender [if available], practice setting [community or hospital pharmacy], experience with MTX in the once-weekly indications [number of patients dispensed with MTX])
- Variables related to awareness of the patient card
- Variables related to awareness of the visual reminder on the outer packaging of oral and parenteral MTX-containing products
- Variables related to pharmacist knowledge of the patient card, the visual reminder on the outer packaging and the need to mark the day of intake for indications requiring once-weekly dosing regimens

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- Variables related to the performed marking of the day of intake of MTX on the outer packaging for indications requiring once-weekly dosing regimens

Variables collected through the patient survey:

- Variables related to the patients treated with MTX (patient age range, gender [if available], length of MTX treatment, indication for MTX treatment, prescriber setting [at first prescription], prescriber specialty [at first prescription and in case of prescriber switching]), and mode of administration of MTX-containing products (oral/parenteral)
- Variables related to receipt and awareness of the patient card, and knowledge of the purpose of the patient card
- Variables related to patient's awareness of the boxed warning in the package leaflet
- Variables related to patient's awareness of the visual reminder on the outer packaging of oral and parenteral MTX-containing products
- Variables related to patients' knowledge of the once-weekly dosing frequency of MTX in the treatment of inflammatory diseases for his/her indication, knowledge of the boxed warning in the package leaflet and visual reminder on the packaging of oral and parenteral MTX-containing products, and knowledge of symptoms of MTX overdose

Data sources:

The survey is a primary data collection study conducted through questionnaires administered by web to prescribers, pharmacists and patients. Prescribers will be identified and recruited via OneKey lists (IQVIA). Pharmacists will be identified and recruited via IQVIA's vendor M3 Global Research. Patients will be identified and recruited via IQVIA's vendors M3 Global Research and GLocalMind.

Study size:

In each target population (prescribers', pharmacists' and patients' surveys) the sample of 150 completed questionnaires can provide for a given proportion of 50% and a confidence interval (CI) of 95% with a precision of 8%, i.e. that proportion in the target population could be between 42% and 58%. This sample (150) will be split among 5 countries for each of the surveys. An empirical split (from a sample of 150 prescribers, 150 pharmacists and 150 patients) will be implemented to provide questionnaires in each country which is both feasible and statistically interpretable.

Data analysis:

The statistical analysis will be conducted using the Statistical Analysis System (SAS®) software V9.4 or above on Windows™ (SAS Institute, North Carolina, USA). The statistical results of the selected countries will be presented in the same report, overall and per country.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Continuous variables will be described by their number (of valid cases and missing values), mean, standard deviation, and median, first quantile (Q1), third quantile (Q3), minimum and maximum. Categorical variables will be described as the total number and relative percentage per category. These will be the percentage per category.

In case of multiple-choice questions, the frequency of each option provided by the participants will be reported in the statistical results. Different combinations of the answers provided will not be considered.

CIs of 95% will be evaluated, when relevant. the results will be weighted according to the real proportion of prescribers, pharmacists, and patients who in each country in order to accurately reflect the population that the survey seeks to measure.

Milestones

Anticipated start of data collection: 01 January 2022

Date(s) of study progress reports: Not Applicable

Interim report(s) of study results: Not Applicable

Registration in the EU PAS register: 23 December 2021

Study report: 11 September 2022

Manuscript: 11 November 2022

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

5. AMENDMENTS AND UPDATES

Amendment / update number (Protocol version)	Section	Reason for amendment / update
Amendment 1 (Protocol version 1.0)	Section 5: Milestones	The date of registration in the EU PAS register was updated to 23 December 2021.
	Section 7.2: Rationale	Table 2 was updated i.e. the distribution date of the checklist in Poland was modified to 1 month after approval (from 6 months after approval) in line with information received from EMA.
	Section 9.5.3: Sample Weighting	Editorial change: “target specialty” modified to “target population”
	Section 9.7.1: General Considerations	Keywords that are to be used for text mining will not be listed in the SAP, instead they will be mined after data collection, and the approach for deriving these keywords will be described in the SAP.
	Annex 2: List Of Healthcare Professionals	The list of HCPs in Sweden to whom the DHPC was sent to was added.
	Annex 5.3: Assessment of Success (Patient Questionnaire)	The calculation of scores was updated to reflect the changes made in the patient questionnaire.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

6. MILESTONES

The planned dates for key study milestones are:

Milestone	Planned date	Comment
Start of data collection	01 January 2022	Subject to timeline of protocol approval
End of data collection	30 April 2022	
Registration in the EU PAS register	Around one month after the protocol approval	23 December 2021
Study report	11 September 2022	
Manuscript	11 November 2022	

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

7. RATIONALE AND BACKGROUND

7.1 Background

Methotrexate (MTX), a synthetic organic compound (small molecule), formerly known by the name of amethopterin belongs to a group of folate inhibitors and to class III of the Biopharmaceutical Classification System (1). It was introduced initially as an antagonist to folic acid in treating low grade (acute) leukaemia in children (1-2). It has a pleotropic mechanism of action, and is now widely used as a chemotherapeutic, immunosuppressant, anti-metabolite and anti-neoplastic agent in a plethora of medical conditions like cancer (breast cancer, lung cancer, acute lymphoblastic leukaemia, acute myeloid leukaemia, lymphoma, non-Hodgkin's lymphoma, prostate cancer, bladder cancer, head and neck cancer, and osteosarcoma) (1, 3-8), severe forms of resistant autoimmune diseases like psoriasis, rheumatoid arthritis (juvenile and adult), Crohn's disease, multiple sclerosis, polyarticular juvenile idiopathic arthritis (1, 9-15).

Mode of administration of MTX is either oral (as tablets) or as solutions for parenteral (i.e. intravenous, subcutaneous, intramuscular, intrathecal, or intraventricular) injection or infusion respectively (1, 5-6, 16-19). The use of MTX was first approved on 7 December 1953 by the Food and Drug Administration (FDA) (20). However, it was introduced for clinical application since mid-1980s in rheumatoid arthritis where it was not recommended as the first-line therapy due to occurrence of toxicity and adverse events (AEs) (1, 21-22). Methotrexate at high doses and in combination with nonsteroidal anti-inflammatory drugs (NSAID) has a very narrow therapeutic index (reported AEs >10%), thus requiring close monitoring of the patient's health to decrease the risk of toxicity (1, 23).

Perception of MTX changed with the introduction of low dose methotrexate (LDMTX) therapy of RA and psoriasis (as an alternate to corticosteroids) (1), with dosage of 7.5-25 mg/week (5-7.5 mg/week in elderly or frail patients; 15 mg/week in healthy patients, maximum dose of 25 mg/week) that reduced the observed toxicity, occurrence of AEs, improved overall tolerance, efficacy and safety in the lives of patients concerned (1, 5-6, 23-25). Similar ranges were also confirmed by other publications and showed a significantly enhanced effect in RA patients as compared to placebos (1, 26-27). This low dose therapy became the gold standard in the cure of RA and is now routinely used. It belongs to the disease-modifying anti-rheumatic drug category (1, 11, 28). Furthermore, a combination of MTX with other biological drugs (like tocilizumab, infliximab, sulfasalazine, hydroxychloroquine, and anti-tumour necrosis factor [anti-TNF] therapy) is currently used to relieve pain and reduce disease progression as part of the treatment of many severe and resistant forms of autoimmune diseases (1, 29-30). Also, high dose methotrexate (HDMTX) with leucovorin rescue (folinic acid or leucovorin) is most regularly used as a therapeutic intervention in oncology for nearly 3 decades now (1, 23, 31).

Methotrexate toxicity is rare with low dose, correct dosing frequency/schedule and strict adherence to the recommended guidelines (25, 32). Methotrexate administration cycle

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

depends on the type of indication being treated, with a weekly low dose schedule for autoimmune diseases and a weekly high dose schedule for tumour reduction. Inadvertent consumption of prescribed MTX doses daily instead of a single low/high dose once a week can cause serious overdose issues and has been proven fatal in patients being treated for the above indications. To conclude, MTX, either alone or in combination with other biological drugs or anti-cancer agents has been extensively used over the last 60 years to treat a variety of autoimmune disorders and different types of cancers, even in off-label applications (where it is not approved by FDA) with same or greater clinical efficacy and has controlled or minimised risks or side effects than most other synthetic drugs available.

7.2 Rationale

In 2019, a referral procedure (EMEA/H/A-31/1463) under Article 31 of Directive 2001/83/European Commission (EC) based on pharmacovigilance data concluded that further risk-minimisation measures were required for oral and parenteral MTX-containing products that avoid incorrect administration schedules, i.e. inadvertent MTX overdose due to daily instead of weekly use. The review was based on post-marketing spontaneous case reports from EudraVigilance, including analysis of the root causes of medication errors, a stakeholder consultation and literature review.

Table 1 presents details on the approval and dissemination dates at the national level for the EMs across the 5 countries included in this study.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Table 1 Educational Materials' and Labels' Approval and Dissemination dates

RMM	France	Germany	Greece	Poland*	Sweden
Updated SmPC with boxed warning					
Approved date	04 Nov 2020	11 Nov 2020	10 Jun 2021	-	23 Mar 2020
Distributed date	6 months after approval	6 months after approval	6 months after approval	11 Sep 2020	6 months after approval
Updated PIL with boxed warning					
Approved date	04 Nov 2020	11 Nov 2020	10 Jun 2021	-	23 Mar 2020
Distributed date	6 months after approval	6 months after approval	6 months after approval	11 Sep 2020	6 months after approval
Visual reminder inner packaging					
Approved date	04 Nov 2020	11 Nov 2020	10 Jun 2021	-	23 Mar 2020
Distributed date	6 months after approval	6 months after approval	6 months after approval	11 Sep 2020	6 months after approval
Visual reminder outer packaging					
Approved date	04 Nov 2020	11 Nov 2020	10 Jun 2021	-	23 Mar 2020
Distributed date	6 months after approval	6 months after approval	6 months after approval	11 Sep 2020	6 months after approval
Patient card with space for weekday					

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

RMM	France	Germany	Greece	Poland*	Sweden
Approved date	-	-	-	24 Mar 2020	22 Jan 2020
Distributed date	16 Dec 2020	25 Nov 2019	Soon to be completed	6 months after approval	6 months after approval
HCP checklist					
Approved date	Not Applicable	-	Not Applicable	10 Jun 2020	22 Jan 2020
Distributed date	Not Applicable	18 Mar 2020	Not Applicable	1 month after approval	6 months after approval
HCP guide					
Approved date	18 Mar 2021	Not Applicable	May 2020	10 Jun 2020	22 Jan 2020
Distributed date	6 months after approval	Not Applicable	July 2020	1 month after approval	6 months after approval
DHCP					
Approved date	-	-	17 Sep 2019	18 Dec 2019	23 Sep 2019
Distributed date	09 Apr 2020	25 Nov 2019	27 Nov 2019	6 months after approval	6 months after approval

*Dates of submission for regulatory approval

Notes:

1. In Poland, the HCP guide and HCP checklist are present in one document.
2. In countries with available information, the date of distribution will be considered, otherwise we will consider 6 months from the date of approval of the EMs. The approval and distribution dates might be varied for different MAHs in one country; therefore, we have referred to the latest date for the approval and distribution per country in this table.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

As a result of these data the following measures were introduced for all oral and parenteral MTX formulations with at least one indication requiring once-weekly dosing (e.g. rheumatologic/dermatological diseases or Crohn's disease):

- Update of summary of product characteristics (SmPC) section 4.2:
    - Only physicians with expertise in the use of MTX and understanding of the risks related to MTX therapy should prescribe MTX;
    - The recommendation to divide the dose has been removed (also package leaflet section 3);
    - Boxed warning that the product must only be taken/used once-weekly (also package leaflet section 3);
    - Prescribers should ensure that patients or their caregivers will be able to comply with the once-weekly regimen (for oral MTX products only).
- Visual reminder on the outer packaging to take/use the product only once a week with space to mark a weekday for intake/use; for MTX-containing products with at least one indication requiring treatment once a week and an oncologic indication the visual reminder must also include the once-weekly indication
- Visual reminder on the inner packaging that the product must only be taken/used once-weekly; for MTX-containing products with at least one indication requiring treatment once a week and an oncologic indication the visual reminder must also include the once-weekly indication
- Switch from bottle to blister packaging (only oral MTX formulations and over a transition period of 4 years)
- Patient card (only oral MTX formulations) with information on once-weekly dosing regimen and space to write the day of the week
- Update of existing EMs for healthcare professionals (HCPs) (i.e. checklist or guide) (only oral MTX formulations)
- Direct healthcare professional communication (DHPC)

8. RESEARCH QUESTION AND OBJECTIVES

The aim of the current study is to examine the effectiveness of product-specific risk-minimisation measures for MTX, by carrying out a survey to evaluate the impact of European union (EU) label changes for medicinal products containing MTX for weekly administration, with reference to the 2019 referral procedure (refer Section 7.2).

The primary objectives of the study are:

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

1. To determine the extent of prescriber awareness and knowledge of the risk of inadvertent overdose due to daily instead of weekly use and adherence to SmPC recommendations for oral and parenteral MTX-containing medicines with at least one indication requiring once-weekly dosing, with particular focus on the following elements:
    1.1. Receipt and awareness of the DHPC
    1.2. Knowledge of the dosing frequency of MTX in the treatment of inflammatory diseases (e.g. rheumatologic/dermatological diseases or Crohn's disease), by indication
    1.3. Knowledge of the updated posology instructions and boxed warning
    1.4. Receipt and awareness of the new or updated EMs for HCPs (checklist or guide) and awareness of the patient card to avoid the risk of inadvertent overdose due to daily instead of weekly use
2. To determine the extent of pharmacist awareness and knowledge of the patient card, the visual reminder on the outer packaging and the need to mark the day of intake for indications requiring once-weekly dosing regimens, and adherence to marking the day of intake on the outer packaging
3. To determine the extent of patient awareness and knowledge of the following elements introduced to avoid incorrect administration schedules for oral and parenteral MTX-containing medicines with at least one indication requiring once-weekly dosing:
    3.1. Receipt and awareness of the patient card, and knowledge of symptoms of MTX overdose and the purpose of the patient card (i.e. to note the day of intake for indications requiring once-weekly dosing regimens, and steps to be taken if symptoms arise, and to alert any HCP not familiar with MTX treatment about the once-weekly dosing regimen e.g. on hospital admission, change of care etc.)
    3.2. Knowledge of the once-weekly dosing frequency of MTX in the treatment of inflammatory diseases (e.g. rheumatologic/dermatological diseases or Crohn's disease), for his/her indication
    3.3. a) Awareness and knowledge of the visual reminder on the packaging of oral and parenteral MTX-containing products; b) Awareness and knowledge of the boxed warning in the package leaflet.

9. RESEARCH METHODS

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

9.1 Study Design

This study is a cross-sectional, multinational, and multichannel survey based on primary data collection conducted among prescribers, pharmacists and patients in 5 selected European countries (France, Germany, Greece, Poland, and Sweden), where there are a sufficient number of eligible prescribers, pharmacist and patients with MTX experience. The survey is designed to examine the impact of EU label changes for medicinal products containing MTX for weekly administration.

9.1.1 Study Period

The data collection period will last about 12 weeks in each country for prescribers, pharmacists and patients surveys. The fieldwork in each country will only start after the EMs have been distributed in each country to enable the assessment of EM effectiveness. Generally, a 6 to 12-month period is considered after the distribution of the EM to allow for full implementation of the risk-minimisation measures (RMMs). Accordingly, the survey start date will begin approximately 18 to 24 months after the date of distribution of the EM in the individual countries listed for evaluation within this protocol. This date may vary by country, based on the date of EM approval by the local Health Authority. The survey will be conducted in outpatient settings through a web questionnaire. To ensure that the invitation and survey are comprehensible, all outreach will be conducted in the local language of each country.

9.2 Setting

The study will enrol prescribers, pharmacists and patients from France, Germany, Greece, Poland, and Sweden over an approximate 12-week time period. However, this time period can be extended if the target numbers are not achieved.

The 5 countries were selected based on the following criteria:

- Representativeness in term of largest MTX sales in Europe (Table 2)
- Representativeness in term of small and large countries
- Representativeness in term of different health care systems
- Representativeness in term of geographical spread across Western, Southern, Northern and Eastern European countries

As per European Medicines Agency (EMA) requirement, the study should be carried out in at least 5 European Economic Area (EEA)/EU countries.

Considering this requirement for diverse geographic representation of European countries, we applied an additional criterion of selection based on the use of MTX in European countries. In the selected countries there will be enough eligible prescribers, pharmacist and

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

patients with MTX experience to participate in the study. We used the unit volume of sales of MTX as a proxy to assess the prevalence of patients or eligible HCPs having experience with the drug (Table 2). Applying these criteria, we proposed the study to take place in the following 5 countries: France, Germany, Greece, Poland, and Sweden. Although, Italy was initially proposed in the proposal, it was replaced by Greece because of a lengthy regulatory and ethics process. If the target sample size is not achieved in one of the selected countries, the possibility of selecting an alternative country will be explored.

Table 2 The Proportions of Methotrexate Sales in 2020 in the European Market*

Countries	The proportions of methotrexate sale	Selected for the study
Austria	1.0 %	
Belgium	5.6%	
Bosnia	0.4%	
Bulgaria	0.7%	
Croatia	1.1%	
Czech Republic	3.5%	
Estonia	0.7%	
Finland	2.1%	
France	11.2%	X
Germany	10.9%	X
Greece	5.4%	X
Hungary	2.2%	
Ireland	2.9%	
Italy	7.0%	
Latvia	0.3%	
Lithuania	0.3%	
Luxembourg	0.1%	
Netherlands	0.5%	

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Countries	The proportions of methotrexate sale	Selected for the study
Norway	3.6%	
Poland	10.6%	X
Portugal	4.2%	
Romania	0.5%	
Serbia	2.0%	
Slovakia	1.2%	
Slovenia	0.4%	
Spain	13.4%	
Sweden	7.0%	X
Switzerland	0.9%	
Total	100.0%	

*The relative proportion of sales in European countries was obtained from IQVIA Midas. The denominator for all proportions is the total unit volume of sales of MTX products in the European countries presented in Table 2.

9.2.1 Participant selection

9.2.1.1 Prescriber Selection

Choice of the specialties to include in the survey will be based on the specialties that have been targeted for distribution of the DHPC and educational material (EM) by the relevant national competent authorities in the selected countries, for e.g. specialists including GPs, internists, rheumatologists, dermatologists, gastroenterologists etc. The choice of specialties can be variable between countries. To the extent possible, prescribing patterns will be obtained from IQVIA data assets as supportive evidence to document the choice of specialties. Please refer to Annex 2. List of Healthcare Professionals for a complete list of prescribers who received the DHPC/EMs per country.

In the absence of comprehensive lists of MTX prescribers, the initial sampling frame for the identification of participating prescribers will be based on the list of all prescribers (OneKey, IQVIA, OneKey is an IQVIA managed database with information of health care professionals) in each of the relevant specialties in the targeted country. OneKey databases are constructed and updated through manual and automated means from various sources, including publicly available sources. OneKey is the most comprehensive list of HCPs in the

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

world with very high coverage in most countries (33). Also, in EU PAS Register, it can be seen where OneKey database has been used for other post-authorisation safety studies (PASS) such as EUPAS34465 and EUPAS32142.

Since the study objective is to determine the extent of prescriber awareness and knowledge of the risk of inadvertent overdose due to daily instead of weekly use of MTX, only prescribers who have prescribed in indications requiring once-weekly MTX (in the past 3 months) will be selected. As this information is not available in the lists of prescribers, the survey will be preceded by a set of questions to check the eligibility of prescribers. Among these, it will be asked if the prescriber has prescribed in indications requiring once-weekly MTX in the past 3 months. If the answer is no, the survey will not be administered to that prescriber.

Prescribers will be identified randomly from OneKey lists (IQVIA) which is representative of the target population in all of the countries and specialties. In case the number of prescribers is limited in a country, an invitation will be sent to all of them.

9.2.1.2 Pharmacist Selection

Pharmacists will be recruited via IQVIA's trusted and assessed vendor M3 Global Research (https://www.m3globalresearch.com/) (34-36). M3 Global Research may work with partner panels where appropriate; in such instances, clients are aware and multiple safeguards are employed to ensure data integrity. This includes on-the-spot deduplication using digital fingerprinting technology, as well as sharing of exclusion lists.

For this study, M3 Global Research will be using their proprietary panel in Germany, Spain, Italy, Belgium and Sweden and then working with partners in Greece and Poland.

M3 Global Research adapts its recruitment methodology based on geographies and target groups. For some target groups, a pure online recruitment approach may not suffice or may not be appropriate, such as for hard-to-reach participant targets. In such instances, other recruitment approaches - such as phone-to-web - may be more appropriate. M3 Global Research transparently advises its clients on the recruitment methodologies planned for each project. M3 Global Research has in-house capabilities for telephone recruitment across its locations spanning over 10 markets. In addition, M3 Global Research works with trusted local partners, educates them on all relevant quality standards, and works with these partners to reach hard-to-reach audiences.

- For France, Germany, and Sweden, M3 Global Research will use their International Organisation for Standardisation (ISO) certified panel for recruitment to this online survey and would expect a mix of settings/locations based on natural fall out from our panellists.
- For Poland, M3 Global Research would be using an external preferred supplier who has signed an agreement with them to ensure that they comply with M3 Global Research's ISO standards. For recruitment, M3 Global Research's local team would

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

be pre-recruiting pharmacists to then complete the online survey and would expect a mix of settings/locations based on natural fall out from our panellists.

- For Greece, M3 Global Research would also be using an external preferred supplier who has signed an agreement with them to ensure that they comply with M3 Global Research's ISO standards. For recruitment, M3 Global Research's local team would be using online recruitment and would expect a mix of settings/locations based on natural fall out from our panellists.

M3 Global Research follows an extensive partner vetting process, which meets ISO 26362 International Standard requirements. All partners are carefully selected and presented the standard as well, to ensure all recruiting parties provide the best possible service to the clients. Partners are reviewed by project staff on each project as well as regularly audited by M3 GR's dedicated team. M3 Global Research provides notification to clients in advance when using third party providers.

9.2.1.3 Patient Selection

Patients will be recruited via M3 Global Research and GLocalMind (http://www.glocalmind.com) vendor panel. As an alternative strategy, patients could have been recruited via prescribers, but this approach would have led to a much more elevated fee. We therefore opted for a direct-to-patient approach.

Patient selection by M3 Global Research:

Details on M3 Global Research and their general recruitment methodologies are provided in Section 9.2.1.2.

- For France and Germany, M3 Global research would still use their internal panel of respondents but will also need to supplement their panel with trusted partners.
- For Poland, M3 Global research would be using an external preferred supplier and they would be pre-recruiting patients to then complete the online survey.
- For Greece, M3 Global research would also be using an external preferred supplier and they would be using online recruitment.

M3 Global Research uses a mixed approach for patient recruitment made up primarily of online panel recruitment and then also including social media campaigns, telephone recruitment and can also offer HCP referrals for certain projects. They do not use river sample for recruitment as respondents will not always be on a panel/be verified and they always aim to provide verified respondents.

Patient selection by GLocalMind:

GLocalMind may work with partner panels where appropriate; in such instances, clients are aware and multiple safeguards are employed to ensure data integrity. This includes on-the-spot deduplication using digital fingerprinting technology, as well as sharing of exclusion lists.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

GLocalMind adapts its recruitment methodology based on geographies and target groups. For some target groups, a pure online recruitment approach may not suffice or may not be appropriate, such as for hard-to-reach participant targets. In such instances, other recruitment approaches, such as phone-to-web - may be more appropriate. GLocalMind transparently advises its clients on the recruitment methodologies planned for each project. GLocalMind has in-house capabilities for telephone recruitment across its locations spanning over 10 markets. In addition, GLocalMind works with trusted local partners, educates them on all relevant quality standards, and works with these partners to reach hard-to-reach audiences.

- For Sweden, GLocalMind will use their International Organisation for Standardisation (ISO) certified panel for recruitment to this online survey and would expect a mix of settings/locations based on natural fall out from our panellists.
- For Poland, GLocalMind would be using an external preferred supplier who has signed an agreement with them to ensure that they comply with GLocalMind's ISO standards. For recruitment, GLocalMind's local team would be pre-recruiting pharmacists to then complete the online survey and would expect a mix of settings/locations based on natural fall out from our panellists.

GLocalMind follows an extensive partner vetting process, which meets ISO 26362 International Standard requirements. All partners are carefully selected and presented the standard as well, to ensure all recruiting parties provide the best possible service to the clients. Partners are reviewed by project staff on each project as well as regularly audited by GLocalMind GR's dedicated team. GLocalMind provides notification to clients in advance when using third party providers.

In order to reduce the eventual risk of unavailability of M3 Global Research and/or GLocalMind, IQVIA will line up another vendor to replace M3 Global Research in the time of field work, if required.

9.2.2 Inclusion Criteria

The following criteria must be met in order to be enrolled in the study:

- *For prescriber questionnaire*: Prescribers who have prescribed MTX in a single low dose once a week for indications that require weekly dosing in the past 3 months
- *For pharmacist questionnaire:* Pharmacists who have dispensed MTX in a single low dose once a week for indications that require weekly dosing in the past 3 months
- *For patient questionnaire:* Patients who have been treated with a single low dose once a week for indications that require weekly dosing in the past 3 months

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

9.2.3 Exclusion Criteria

Participants meeting the following criteria are not eligible for participation:

- Prescribers, pharmacists, or patients who declare having a conflict of interest with the survey (i.e. participants employed by regulatory bodies, pharmaceutical industries)
- Prescribers, pharmacists, or patients who do not provide consent for participating in the survey

9.2.4 Study Enrolment

The following groups will be considered as the target population:

- All prescribers within the selected specialties in the selected countries who have prescribed a weekly dose of MTX in the past 3 months
- All pharmacists in the selected countries who have dispensed a weekly dose of MTX in the past 3 months
- All patients in the selected countries who have used a weekly dose of MTX in the past 3 months

The survey will be conducted by IQVIA's Global Primary Intelligence, a division of IQVIA specialised in the conduct of phone and web surveys for more than 20 years. IQVIA's Global Primary Intelligence will create a web-based survey. Prescribers, pharmacists and patients' answers/data will be collected through this web survey. Participants will be randomly contacted, mainly by email, and phone or letter when needed, according to their stratum.

The targeted prescribers will be randomly selected and enrolled on an ongoing basis until the study size is reached (37). Random selection of prescribers and pharmacists is performed to minimise selection bias.

An equal distribution of age, gender and indication for MTX treatment cannot be made throughout recruitment, but a quota can be built into the survey to allow certain numbers for each of these categories. However, this may result in a longer period of recruitment and lower number of respondents. If this is the case, we will remove the quota at some point during the fieldwork, to recruit the pre-defined sample size. It should also be noted that the survey was not designed to provide a representative sample across age categories, gender, or indication for MTX.

9.2.4.1 Prescribers

Prescribers who consent to participate in these types of surveys will be first contacted by email, then by phone if they do not respond to the email. Their recruitment will be done as follows:

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- Prescribers will be invited to participate in the survey via email. The email invitations will contain the link to the web questionnaire. In the invitation, the survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the prescribers at this step. Compensation will be compliant with relevant guidelines of each country and will compensate the actual effort and time needed to fill out the questionnaire.
- If the questionnaire is not completed, the prescribers will be sent a reminder by email one week after the invite was sent out.
- If the target is not achieved, a second reminder by phone will be conducted approximately 1.5 weeks after the invite was sent out.
- If the questionnaire is still not completed, a third reminder will be sent to the prescribers by email approximately 3 weeks after the invite was sent out.

If necessary, i.e. if the target number of responders is still not reached, recruitment will attempt to continue to achieve the targeted study sample size. A prescriber will be considered unreachable if he/she has been contacted between 3 to 5 times without an answer.

For each prescriber selected, the number of times the prescriber was contacted, as well as the date and time when he/she completed the web questionnaire, will be recorded. The recruitment in each target country will be stopped when the target number is reached (see Section 9.2.1.1 for further details on prescriber selection.

The number of prescribers that are eligible for inclusion in the study and the survey response rate will be monitored regularly.

The IQVIA internal field team will support prescribers if they see that the prescribers get stuck during the course of completing the survey, or if the prescribers stop for any reason – they will provide technical help. A free phone number will also be available for prescribers to call.

9.2.4.2 Pharmacists

Pharmacists will be recruited by IQVIA's trusted and assessed vendor, M3 Global Research, from the vendor representative panel. As in the prescribers' surveys, pharmacists will be first contacted by email, then by phone if they do not respond to the email. Their recruitment will be done as follows:

- The sampling of pharmacists will follow a randomised sampling method which ensures the representativeness of the population being reached in order to limit selection bias which is commonly found in opportunistic selection method. However, only pharmacists who consent will participate, which brings some degree of selection bias that cannot be ruled out.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- The M3 Global Research team will randomly contact pharmacists by emails or phone calls when needed, according to their sub-groups (see Section 9.2.1.2 for further details on pharmacist selection). Survey background and objectives, the contact information for questions, and the proposed compensation will be explained at this stage.
- If they agree to participate in the survey, they will receive a link to access the survey and the instructions for web questionnaire completion.
- If the questionnaire is not completed in the IQVIA Primary Intelligence electronic data capture (EDC) system, the pharmacists will be sent regular email/phone reminders.
- The M3 Global Research telephone team can call the pharmacists if they see that they get stuck during the course of completing the survey, or if they stop for any reason – they might provide technical help or other advice. Pharmacists will also have the option to contact M3 directly if they need support. These interactions cannot be scripted.
- A screening log is maintained to follow-up the inclusion of pharmacists in the survey over time.

If necessary, i.e. if the target number of responders is still not reached, recruitment will continue to achieve the targeted study sample size. A pharmacist will be considered unreachable if he/she has been contacted between 3 and 5 times without any answer being received. The number of pharmacists that are eligible for inclusion in the study and the survey response rate will be monitored regularly.

9.2.4.3 Patients

Patient enrolment by M3 Global Research:

Patients in Germany, France and Greece will be recruited by IQVIA's trusted and assessed vendor – M3 Global Research, from the vendor representative panel. As in the prescribers' surveys, patients will be first contacted by email, then by phone if they do not respond to the email. Their recruitment will be done as follows:

- The sampling of patients will follow a randomised sampling method which ensures the representativeness of the population being reached in order to limit selection bias which is commonly found in opportunistic selection method. However, only patients who consent will participate, which brings some degree of selection bias that cannot be ruled out.
- The M3 Global Research team will randomly contact patients by emails or phone calls when needed, according to their sub-groups (see Section 9.2.1.3 for further details on patient selection). Survey background and objectives, the contact

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

information for questions, and the proposed compensation will be explained at this stage.

- If they agree to participate in the survey, they will receive a link to access the survey and the instructions for web questionnaire completion.
- If the questionnaire is not completed in the IQVIA Primary Intelligence EDC system, the patients will be sent regular email/phone reminders.
- The M3 Global Research telephone team can call the patients if they see that they get stuck during the course of completing the survey, or if they stop for any reason – they might provide technical help or other advice. Patients will also have the option to contact M3 directly if they need support. These interactions cannot be scripted.
- A screening log is maintained to follow-up the inclusion of patients in the survey over time.

If necessary, i.e. if the target number of responders is still not reached, recruitment will continue to achieve the targeted study sample size A patient will be considered unreachable if he/she has been contacted between 3 and 5 times without any answer being received.

The number of patients that are eligible for inclusion in the study and the survey response rate will be monitored regularly.

Patient enrolment by GLocalMind:

Patients in Sweden and Poland will be recruited by IQVIA's trusted and quality assessed vendor – GLocalMind, from the vendor representative partner panel.

Patients will be first contacted via both email and GLocalMind's panellist member app (linked to their panel portal), then by phone if they do not respond to the email and app. Their recruitment will be done as follows:

- The sampling of patients will follow a randomised sampling method which ensures the representativeness of the population being reached in order to limit selection bias which is commonly found in opportunistic selection method. However, only patients who consent will participate, which brings some degree of selection bias that cannot be ruled out.
- The GLocalMind team will randomly contact patients by emails or via their app when needed, according to their sub-groups. Survey background and objectives, the contact information for questions, and the proposed compensation will be explained at this stage.
- If they agree to participate in the survey, they will receive a link to access the survey and the instructions for web questionnaire completion.
- If the questionnaire is not completed, the patients will be sent a reminder by email one week after the invite was sent out.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- If the target is not achieved, a second reminder by phone will be conducted approximately 1.5 weeks after the invite was sent out.
- The GLocalMind telephone team can call the patients if they see that they get stuck during the course of completing the survey, or if they stop for any reason – they might provide technical help or other advice. Patients will also have the option to contact GLocalMind directly if they need support. These interactions cannot be scripted.
- A screening log is maintained to follow-up the inclusion of patients in the survey over time.

If necessary, i.e. if the target number of responders is still not reached, recruitment will continue to achieve the targeted study sample size A patient will be considered unreachable if he/she has been contacted between 3 and 5 times without any answer being received.

The number of patients that are eligible for inclusion in the study and the survey response rate will be monitored regularly.

9.2.4.4 Selection criteria of the booster country

When the list (prescribers, pharmacists or patients) is exhausted in any target country (France, Germany, Greece, Poland, and Sweden) at any given time during the recruitment period and the overall sample size is not yet reached, recruitment will take place from another country from the list of target countries, to achieve the overall sample size.

The following criteria need to be fulfilled by the booster country, from the list of the participating countries in this survey, in order for further recruitment to take place:

- Any other country which meets the minimum sample size
- The list of prescribers, pharmacists or patients in that country is not yet exhausted

At this point, it is not possible to project which country(ies) may be suited to boost an exhausted country(ies), hence the above criteria will be followed to select suitable booster countries.

9.3 Variables

9.3.1 Exposure Definition and Measures

No study medication is provided as part of participation.

9.3.2 Outcome Definition and Measures

The number of prescribers/pharmacists/patients invited to participate will be managed through the computer software, which is used to send and manage the invitations, but not through the survey as such. After fieldwork completion we will provide a separate report containing recruitment data that can be used to analyse the participation rate.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

9.3.2.1 Variables collected through the prescriber survey

The following variables will be collected through the prescribers' surveys:

- Variables related to prescriber's practice information:
  - Demographic information (country)
  - Gender (if available)
  - Prescriber primary specialty
  - Duration of practice in primary specialty (inclusive of specialty trainings)
  - Practice setting (Office or hospital-based or both)
  - Experience with MTX in the once-weekly indications (number of patients treated with MTX)
- Variables related to the prescriber's receipt and awareness of the DHPC and EMs:
  - Receipt and awareness of the DHPC
  - Receipt and awareness of the new or updated EMs for HCPs (checklist or guide)
  - Awareness of the patient card
- Variables related to the knowledge of the risks of inadvertent overdose due to daily instead of weekly use
  - Knowledge of the dosing frequency of MTX in the treatment of indications requiring once-weekly dosing regimens
  - Knowledge of the updated posology instructions and boxed warning
- Variables related to adherence to SmPC recommendations for oral and parenteral MTX-containing medicines with at least one indication requiring once-weekly dosing

9.3.2.2 Variables collected through the pharmacist survey

The following variables will be collected through the pharmacists' surveys:

- Variables related to pharmacists' practice information:
  - Demographic information (country)
  - Gender (if available)
  - Practice setting (community or hospital pharmacy)

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- Experience with MTX in the once-weekly indications (number of patients dispensed with MTX)

- Variables related to pharmacist's awareness of the patient card
- Variables related to awareness of the visual reminder on the outer packaging of oral and parenteral MTX-containing products
- Variables related to pharmacist knowledge of the patient card, the visual reminder on the outer packaging and the need to mark the day of intake for indications requiring once-weekly dosing regimens:
  - Knowledge of the patient card
  - Knowledge of the visual reminder on the outer packaging
  - Knowledge of the need to mark the day of intake for indications requiring once-weekly dosing regimens
- Variables related to the performed marking of the day of intake of MTX on the outer packaging for indications requiring once-weekly dosing regimens

9.3.2.3 Variables collected through the patient survey

The following variables are collected through the patient survey:

- Variables related to the patients treated with MTX
  - Patient age range
  - Gender (if available)
  - Length of MTX treatment
  - Indication for MTX treatment
  - Prescriber setting (at first prescription) and prescriber specialty (at first prescription and in case of prescriber switching)
  - Mode of administration of MTX-containing products (oral/parenteral)
- Variables related to the patient card:
  - Receipt and awareness of the patient card
  - Knowledge of the purpose of the patient card
- Variables related to patient's awareness of the boxed warning in the package leaflet
- Variables related to patient's awareness of the visual reminder on the outer packaging of oral and parenteral MTX-containing products

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- Variables related to patient's knowledge of the once-weekly dosing frequency of MTX in the treatment of inflammatory diseases:
    - Knowledge of the once-weekly dosing frequency of MTX in the treatment of inflammatory diseases for his/her indication
    - Knowledge of the boxed warning in the package leaflet and visual reminder on the packaging of oral and parenteral MTX-containing products
    - Knowledge of symptoms of MTX overdose

9.3.3 Safety Measures

Not applicable.

9.3.4 Effectiveness Measures *(If Applicable)*

Not applicable.

9.3.5 Other Measures *(If Applicable)*

Not applicable.

9.4 Data Sources

The survey is a primary data collection conducted through 3 questionnaires administered by web:

- A prescriber questionnaire
- A pharmacist questionnaire
- A patient questionnaire

9.4.1 Questionnaire description

The questionnaires will have a disclaimer and consent in the beginning. It collects information on demographics and eligibility of participants. It has included closed questions on the content of the EM, the question will be in order from the simplest to the hardest and from awareness to implementation. Furthermore, it is non-directing and not favouring social desirability, there is no possibility of coming back on previous answers to avoid information bias.

9.4.2 Qualitative interviews

Prior to initiation of the survey, IQVIA conducted qualitative interviews with 3 prescribers (2 from Germany and 1 from Sweden) and 3 pharmacists (2 from Germany and 1 from

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Sweden) in English language . Also, 3 patients were interviewed by IQVIA's trusted and assessed vendor, GLocalMind, (2 from France and 1 from Germany) in the local language. These interviews were carried out to gather more insights into the elements impacting the awareness, knowledge and behaviour of the population targeted with the risk-minimisation measures. The details of this qualitative approach were used as inputs to develop the protocol and the survey questionnaires (Annex 4. Summary of Qualitative Interviews).

9.4.3 Questionnaire development

Each questionnaire i.e. prescriber, pharmacist and patient questionnaire was developed in English. The questionnaires were designed to be non-directing, clear, to avoid inducement of social desirability and had no self-evident answers. Each questionnaire included questions about screening criteria, demographics, receipt and awareness of MTX EMs, and knowledge about MTX risks. The prescriber and pharmacist questionnaire had additional questions about self-declared behaviour.

9.4.4 Questionnaires translation

The translated versions of each questionnaire from English into local language will be done using the back and forth method (from English into local language and then from local language into English) to ensure an accurate translation. They will be then submitted to EMA for review and approval. Translation and back translation will be performed..

9.4.5 Questionnaire pilot testing

The objective of the prescriber and pharmacist questionnaires will be tested among 3 prescribers and 3 pharmacists, respectively, to make sure the right language and medical terms are used. The patient questionnaire will be tested by 3 non-physicians to check the understandability of the language.

9.4.6 Time to completion

Each prescriber, pharmacist and patient questionnaire's completion is estimated to take 10-15 minutes each.

9.4.7 Approaches for increasing response rates

People are increasingly contacted to participate in web or phone surveys. The overall response rate of participation remains low according to international studies (38-40). Holbrook et al. showed that the response rate to surveys continues to decline over time, but a lower rate does not appear to reduce the representativeness of a demographic survey (39). VanGeest et al. conducted a systematic review of 66 published reports on efforts to perform for improving response rates (41). Two general strategies were explored: incentives-based approaches and survey design-based approaches. Financial incentives, even little ones, were effective in improving physician response rates while non-monetary incentives were much

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

less effective. These measures include the use of a short questionnaire, and questionnaires personalised, and approved by professional associations.

In order to increase the response rate among prescribers, pharmacists or patients, a compensation fee will be proposed to prescribers, pharmacists or patients for their participation in the survey.

9.5 Study Size

9.5.1 Target Sample Size Calculations

The sample size formula based on the normal approximation to the binomial is the following:

$$n = \frac{P \cdot (1-P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where P is the expected proportion, and e is the precision or the desired margin of error reflecting how many percentage points the results will differ from the real population value. For example, a 95% confidence interval (CI) with an 8% margin of error means that the statistic will be within 8 percentage points of the real population value 95% of the time. Z1- α/2 is the standard normal Z value corresponding to a cumulative probability of 1 – α/2 and reflecting the confidence level that will be used (e.g. if α =.05 (i.e. 5% level of significance) then Z = 1.96). The range of p is between 0 to 1, and therefore the range of p(1-p) is between 0 to 1. The value of p that maximises p(1-p) is p = 0.5. Consequently, if there is no information available to approximate p, then p = 0.5 (i.e. 50%) can be used to generate the most conservative i.e. largest sample size.

Table 3 Margin of Error for 95% CI Based on Various Sample Sizes and Proportions of Interest

Margin of error for 95% CI (absolute precision)							
Proportion	**8%**	**7%**	**6%**	**5%**	**4%**	**3%**	**2%**
10%	55	71	97	139	216	384	864
30%	127	165	225	323	504	896	2,017
50%	150	196	267	384	600	1,067	2,401
70%	127	165	225	323	504	896	2,017
90%	55	71	97	139	216	384	864

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

CI = confidence interval.

In each target population (prescribers, pharmacists and patients) the sample of 150 completed questionnaires can provide for a given proportion 50% and a confidence interval of 95% with a precision of 8%, i.e. that proportion in the target population could be between 42% and 58%. This sample (150) will be split among 5 countries for each of the surveys.

9.5.2 Sampling in the Participating Countries

Ideally the sample of 150 prescribers, 150 pharmacists and 150 patients should be split among the countries based on the proportion of each target population (Table 4). However, such a sample distribution would lead to a too small number in some countries and a too large number in some others. As an alternative, an empirical split will be implemented to provide a number of questionnaires in each country which is both feasible and statistically interpretable. Such a sample will necessitate that the results of the study be weighted according to the real proportion of each target population in the countries.

Table 4 Indicative Sample Distribution

Country	Prescribers	Pharmacists	Patients
France	30	30	30
Germany	30	30	30
Greece	30	30	30
Poland	30	30	30
Sweden	30	30	30
Total	150	150	150

9.5.3 Sample Weighting

Since the relative weight of each country in the final sample will be different from its real relative weight in estimations, the extrapolation of the raw survey results to the overall target population would not be relevant without weighting. The survey results will be then weighted to reflect the real proportion of the prescribers, pharmacists, or patients in participating countries (or group of countries). Both unweighted (i.e. raw data) and weighted results will be presented in the report.

A weight variable will be applied to each statistical unit (i.e. a completed questionnaire) during the results calculation in order to correct any over-or under-sampling that may have

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

occurred for a country or a target population. This weight variable will indicate how many unit(s) of the population of interest an observation will count in a statistical procedure. Its value will change per country and per target population. The weights will be normalised to obtain their sum for the whole dataset that will be equal to the sample size.

Since the weighted results are intended to represent their corresponding target population, the weighted results shall be used whenever available in the report. Unweighted results that ignore the sample weight can be biased for population quantities. But for more transparency, both unweighted and weighted results will be presented in the report. For the subsample information, the weighted results will not be provided as they do not make sense. As weighting is a statistical extrapolation by itself, it can only be conducted under the circumstances that such an extrapolation is valid. In the case of subsamples where the numbers are too low to be extrapolated for example, it makes sense not to weight. Therefore, the unweighted numbers which describe the sample – rather than the population – shall be used.

9.6 Data Management

The survey will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA Primary Intelligence and IQVIA Real World Evidence Solutions.

As the questionnaire is simple and short a single data entry will be sufficient. Collected data will be entered and stored in a database specific to the survey and the country. A study database will be created by merging of databases of each country.

Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required);
- Data labelling and data formatting;
- Range and consistency checks for each variable to identify potential non- admissible values;
- Cross-check the consistency of data for related variables (if feasible);

The study database will be locked once validated.

9.6.1 Data Entry/Electronic Data Capture

The data will be self-entered by the participating prescriber, pharmacist, or patient.

The survey will be conducted according to the SOPs of IQVIA Primary Intelligence and IQVIA Real World Evidence Solutions. Data will be collected using an EDC system (Merphin) developed following a full validation process. A rigorous System Development Life Cycle is used for validation that complies with internal IT SOPs of Primary Intelligence (IQVIA).

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Unit testing and formal validation will occur on all appropriate systems and components during the build stage. The internet-based repository will be used to store survey data and other relevant programme information. Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead without answering the previous question. Programming will be reviewed by Quality Control and simulated users (User Testing) prior to implementation.

9.6.2 Source Documents

Not applicable.

9.6.3 File Retention and Archiving

The study documentation will be archived internally at IQVIA. The web questionnaires data will be stored on the survey database for 12 months.

Data storage will be in line with national data protection requirements for each of the countries where the study will be conducted.

All other documentation pertaining to the study, including paper and electronic records will be retained for a minimum of 5 years after the end of the study, in accordance with IQVIA SOPs.

9.7 Data Analyses

The statistical analyses will be described and further detailed into a Statistical Analysis Plan (SAP). The described analysis below might be revised, and adjustments might occur. The final SAP version will include (empty) table shells to be populated for the clinical study report.

9.7.1 General Considerations

The statistical analysis will be conducted using the Statistical Analysis Software (SAS®) software V9.4 or above on Windows™ (SAS Institute, North Carolina, USA).

Continuous variables will be described by their number (of valid cases and missing values), mean, standard deviation, and median, Q1, Q3, minimum and maximum. Categorical variables will be described as the total number and relative percentage per category. These will be the percentage per category. In case of multiple-choice questions, the frequency of each option provided by the prescribers, pharmacists, and patients will be reported in the statistical results. Different combinations of the answers provided will not be considered. Confidence intervals of 95% will be evaluated, when relevant. Variables with free text options will be analysed by text mining method to extract and identify meaningful

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

information. Detailed information on the approach for deriving keywords for text mining will be described in the SAP.

The proportions of correct and appropriate answers to selected questions asked in the questionnaire will be expressed among prescribers, pharmacists, and patients who provided answers to those questions (the missing data will not be counted as a denominator in proportions). The endpoint will be assessed overall, by country for the 3 surveys. In a first step, calculations will be performed on raw data. No projection factor will be applied to generalise the results to the entire participants' universe. Consequently, the line "Overall - unweighted results" will show only the results observed on the overall sample and will not reflect the countries' universe since this sample is not proportional to the size of the lists in each country. In a second step, the results will be weighted according to the real proportion of prescribers, pharmacists, and patients in each country in order to accurately reflect the population that the survey seeks to measure.

9.7.2 Planned Analyses

9.7.2.1 Analysis of Participation Rate

The following different cases of total responses and non-responses will be distinguished and analysed for prescribers, pharmacists and patients:

- Prescribers, pharmacists or patients who did not participate (R): Prescribers, pharmacists or patients who did not respond or that explicitly indicated their refusal to participate (if available)
- Prescribers, pharmacists or patients with partially answered questionnaires (P): Prescribers, pharmacists or patients who clicked on the link provided in the invitation email, and who began answering the questionnaire but never submitted it
- Prescribers, pharmacists or patients with completed questionnaire (C): Prescribers, pharmacists or patients who completed the entire questionnaire
- Contacted prescribers, pharmacists or patients: Prescribers, pharmacists or patients who were reached by phone or who received a web link to the online survey via email OR patients who received a web link to the online survey via email = C+P+R
- Prescribers, pharmacists or patients who agreed to participate: Prescribers, pharmacists or patients who participated in the survey (e.g.by clicking on the link provided in the invitation email) = P+C
- The prescribers', pharmacists' and patients' participation in the survey were examined as follows:
    - Response rate = C/(C+P+R)
    - Refusal rate = R/(C+P+R)

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

The participation rates will be presented by country.

9.7.2.2 Questionnaire Analysis

The statistical results of the selected countries will be presented in the same report, overall, per country.

The general statistical considerations described above (Section 9.7.1) will be applied for quantitative and qualitative variables. The numbers of missing data will be indicated. Missing values are expected to be few and distributed at random. Since there is no applicable method unanimously accepted, there will be no replacement or imputation of missing data (42). Confidence intervals of 95% will be evaluated for endpoint variables.

Analysis for the survey will be performed for patients, prescribers, and pharmacists separately for the endpoints described below:

- **Awareness** will be assessed through the percentage of
    - prescribers who receive and/or are aware of the DHPC, HCP guide, HCP checklist and patient card
    - pharmacists who are aware of the patient card and visual reminder on the outer packaging
    - patients who receive and/or are aware of the patient card, the boxed warning in the packaging leaflet, and visual reminder on the outer packaging
- A **knowledge** score will be created to summarise all responses at individual prescriber, pharmacist, and patient level. An individual prescriber/pharmacist/patient score is calculated as the proportion of correct responses among all questions related to knowledge
- A **self-declared behaviour** score will be created (for prescribers and pharmacists) to summarise all responses at individual physician level. An individual prescriber/ pharmacist score is calculated as the proportion of desriable responses among all questions related to self-declared behaviour.

The number and relative percentage of prescribers/pharmacists/patients who have provided correct answer to each of the questions and then number and relative percentage of prescribers/pharmacists/patients with correct responses to 70%, 80%, 90% and 100% of all the questions will be described.

Assessment of success

In each of the 3 surveys, the proportion of correct or desirable responses across all questions related to the evaluation of the objectives of the surveys will be considered to assess the success.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

The questions considered as complementary will not be included in the assessment of success. The details of the assessment of the success for each survey and each objective is described in Annex 5.

Success at the prescriber, pharmacist, patient level will be defined for each objective based on the number of sub-questions related to that objective being answered correctly or desirably. It is proposed to set the threshold to at least 80% of knowledge questions, including sub-questions, are completed with correct/desirable answers. .

A threshold of 80% successful prescribers/pharmacists/patients on each of the outcomes of awareness, knowledge and self-declared behaviour (self-declared behaviour is not for patients) would be considered appropriate for assessing the effectiveness of RMM.

If additional information from published literature becomes available at the time of reporting, then the results will be discussed in the context of this new information. The methods of reporting and analysis of results obtained will be done as already described in the Protocol and will be further detailed in the SAP.

Profile of prescribers/pharmacists with incorrect answers

The profile of prescribers/pharmacists with incorrect answers to questions related to the main objectives (awareness, knowledge, and self-declared behaviour) will be described using all available and relevant prescribers'/pharmacists' characteristics collected in the survey (i.e., country, specialty, duration of practice, practice setting, prescribing/dispensing volume, age and gender).

Profile of patients with incorrect answers

The profile of patients with incorrect answers to questions related to the main objectives (awareness and knowledge) will be described using all available and relevant patient characteristics collected in the survey (i.e., country, age range, indication).

9.7.3 Exploratory Analyses (If Applicable)

Not applicable.

9.7.4 Handling of Missing Data

The web questionnaire will be programmed in such a way that participants cannot skip questions. We thus do not expect missing values in submitted questionnaires, and neither replacement nor imputation of missing data is expected to be required. Since there is no applicable method unanimously accepted, there will be no replacement or imputation of missing data.

However, on the rare occasion that a system bug may occur and lead to a missing answer in a crucial screener question or a question that is part of the assessment of success, and it is

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

not possible to obtain the missing answer through the quality control process as outlined in Section 9.8, the whole questionnaire will be dropped.

9.8 Quality Control

9.8.1 Data collection, validation and data quality control

Data will be collected using a web-administered questionnaire to physicians, pharmacists and patients. The survey will be conducted according to the SOPs of IQVIA Primary Intelligence and IQVIA Real World Evidence Solutions.

Data will be collected using an EDC system developed following a full validation process. A rigorous System Development Life Cycle that complies with IQVIA Primary Intelligence information technology SOPs is used for validation. The programmed survey will be tested and validated in accordance with IQVIA SOPs, which cover validation for all clinical and risk management-related applications. The internet-based repository will be used to store survey data and other relevant program information. Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead without answering the previous question. Response options presented in a list are randomised to minimise positional bias. Programming will be reviewed by Quality Control and simulated users (User Testing) prior to implementation.

Collected data will be entered and stored in a database specific to the survey and the country. A study database will be created by merging of databases of each country. Prescribers, pharmacists and patients identifying information will be stored separately from survey data.

9.8.2 Approaches for validating the results

The quality control for validating the results will be conducted at 5 levels:

1. Every effort will be undertaken to collect complete and valid data.
2. At the study database level, final data quality checks will be applied to count the number of inconsistent values and estimate the associated relative percentage.
3. At the statistical analysis level: all data management and statistical analysis programmes developed and used in the analysis will be documented.
4. At the results level, a data review will be done to ensure data integrity.
5. At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real World Evidence Solutions and Primary Intelligence divisions. The

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

study documents have been approved by people competent in medical and safety areas of IQVIA. According to the SOPs, an independent review of the survey results and report will be conducted by a person who was not in charge of their preparation.

9.8.3 Safeguards, security and traceability of contacts

Operators of the call centre specialised in health surveys will be assigned to the project and trained on the survey methodology prior to fieldwork. The email contacts will be captured in the internal IQVIA and vendor booking systems.

Participating prescribers/pharmacists/patients will access the online survey via a secure link. This link is unique to each HCP/patient.

The answers provided will be collected in an anonymous way.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time and will include security elements to prevent anyone other than authorised staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A copy of the database and the application files will be made outside the server housing the web-based study. These copies for security purposes will be periodically made and stored outside this server.

9.9 Limitations of Research Methods

9.9.1 Bias

Selection bias:

a) Prescribers

The potential for selection bias of prescribers participating in a survey is an inherent limitation to any study based on volunteer participation. For instance, it is possible that prescribers willing to participate in the study will have the highest awareness of risks associated with use of MTX. To quantify the selection bias, the distribution of sociodemographic characteristics of prescribers (country, specialty, years of practice, gender etc.) will be compared between participants and non-participants.

b) Pharmacists and Patients survey

For pharmacists and patient, recruitment will be through M3 Global Research from the vendor panel; only pharmacists and patients who consent to participate will be surveyed which means that selection bias cannot be ruled out. Also, patients with high health consciousness and higher awareness might participate in the survey. Since the vendor does not collect any personal data from non-respondence, it would not be possible to rule out any selection bias.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Information bias:

Bias in the questionnaire's completion

Recall bias may lead to an underestimation of the prescribers recalling having received EMs. To comment about these differences in accuracy or completeness of the recollections retrieved when answering the survey, if any, we will include updated information about the distribution of EMs in each participating country in the questionnaires for each stakeholder group. To prevent recall bias for prescribers and pharmacists, they will be recruited in the survey if they prescribe or dispense once-weekly dose of MTX in the past 3 months.

Limits Inherent to Web Surveys

In such surveys, the generalisation and external validity of the results is restricted to prescribers who have an active email address and willing (and able) to answer a questionnaire online. These prescribers may not be fully representative of the whole targeted population (43).

Among non-response bias, targeted prescribers may also have activated filters in their mailbox in order to block spams and unsolicited emails. They may not even see the invitation to participate in the survey if a very strict degree of message filtering is set. Having multiple email addresses could also be a critical situation. If the one used is not the primary address or if the prescribers do not check their email box frequently, they will not receive the invitation during the recruitment period. Some HCPs who were sent a letter may not have received it. This is one of the reasons why the HCPs will also be contacted by phone.

Moreover, web surveys may promote social desirability bias which refers to the tendency of prescribers to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour, e.g. prescribers can copy-paste information gathered online instead of giving their own opinions (43). Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire could/tends to reduce this bias (44). The access to the web questionnaire interface will be strictly limited to the invited participants, with the possibility to participate only once and a traceability system. Thus, stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfil the survey in order to influence the results) or unverified respondents (when it is not possible to verify who responds) are not applicable.

9.9.2 Limitations of Pharmacists and Patients Panels

Pharmacists and patient panels may not be representative of the general population of pharmacists and patients especially in terms of age (elderly patients are less proficient with using the internet than younger patients).

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

9.9.3 Generalisation of the Survey Results to the Overall Target Population

Although the raw survey results cannot be generalised to the overall target population, we implement a sample adjustment which allows the generalisation of the results. For more transparency and accuracy, both unweighted (i.e. raw data) and weighted results will be presented in the report.

9.9.4 Apprasial of Medical Errors

Medical errors can often occur by prescribers/pharmacists who have not yet prescribed/dispensed MTX in a single low dose once a week, for indications that require weekly dosing. However, these types of medical errors are quite difficult to measure and the current survey is not designed to measure them.

9.10 Other Aspects

9.10.1 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant independent Ethics Committee for approval or favourable opinion, if applicable. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained.

9.10.2 Study Management

This study will be performed by IQVIA including development of materials, recruitment, training and management of sites, EDC and data management and analysis.

9.10.3 Study Governance *(If Applicable)*

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential. Only aggregated data will be analysed and communicated in a report. The study will be conducted in agreement with the regulation (EU) 2016/679 of the European Parliament on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation).

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

10.1 Participant Information and Informed Consent

Prescribers, pharmacists, and patients participating in the survey will be informed about the targets of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to use their data or to IQVIA (for pharmacists and patients survey, M3 Global Research will keep the personal data) keeping their data. IQVIA will ensure that the national and European data protection and ethical requirements are met for the prescribers, pharmacists, or patients, whenever applicable. This will be done electronically.

10.2 Participant Confidentiality

Data confidentiality / Data security

Participants will access the website (https: secured site) via a personal secure link. This link is unique to each participant.

Only aggregated data and presented as a synthesis will be transmitted to the EMA.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time and will include security elements to prevent others than authorised staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A security copy of the database and the application files will be made outside the server housing the web-based study. Security copies will be periodically made and stored outside this server.

Description of all elements of security and traceability will be available upon request.

10.3 Independent Ethics Committee/Institutional Review Board

The survey will follow the regulatory and ethical requirements of each country. The survey will comply with the module VIII of the good pharmacovigilance practices (GVPs). Although EU Pharmacovigilance Directive (DIR 2010/84/EU) is a legal act, it does not carry the same binding force of a Regulation; each Member State can determine how best to transpose the Directive into local legislation. As a result, the submission requirements for PASS consisting in survey vary throughout the EU, with some countries being more onerous than others. IQVIA includes experts dedicated to the review and advisement on the regulations and guidelines applicable to this study in the participating countries. As this survey is about collection of opinions rather than healthcare data, it is technically considered as a market research in most countries. IQVIA will follow the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines (45).

The regulatory requirements in each participating country are summarised in Table 5.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Table 5 Country-specific ethical approvals

Country	Competent Authority notification	Ethical approval
France	Authority notification is required for information only. Additionally, notification to the National Medical Council (CNOM) and Notification to order of Pharmacists is required.	Not required
Germany	Authority notification is required, acknowledgement from Authority is required. Timeline for review is 30 days. In addition, notification is required to the following regulatory bodies: The Federal Panel Doctors' Association (KBV), The Central Federation Association of the Statutory Health Insurance Fund (GKV) and Association of the Private Insurance (PKV).	Not required
Poland	Authority notification is required for information only.	National Ethics Committee approval is required. Timeline for review is 30 days.
Sweden	Authority notification is required for information only.	Not required
Greece	Authority notification is required for information only.	Not required

10.4 Compensations

Prescribers, pharmacists, and patients will be offered a compensation for the time spent participating in this survey (that they may refuse). The time to complete the survey is estimated between 10-15 minutes.

The amount of this compensation will be determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies (ASOCS) charter, and which states:

"When it is necessary to compensate an HCP in return for the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the HCP for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the HCPs' participation in the survey. They must be declared to the tax authorities in accordance with applicable laws".

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

It should be noted that this study is not designed to collect information on individual AEs. In the event any adverse reactions to MTX are identified during the study, survey participants will be referred to the national medicines regulatory authorities for reporting adverse reactions, as follows:

- Germany: Federal Institute for Drugs and Medical Devices (Email: poststelle@bfarm.de; Website: www.bfarm.de), and Paul Ehrlich Institute (Email: pei@pei.de; Website: www.pei.de)
- Sweden: Medical Products Agency (Email: registrator@mpa.se; Website: www.lakemedelsverket.se)
- France: The French National Agency for Medicines and Health Products Safety (Email: communication.ANSM@ansm.sante.fr; Website: www.ansm.sante.fr)
- Greece: National Organisation for Medicines (Email: inter.rel@eof.gr; Website: www.eof.gr)
- Poland: Chief Pharmaceutical Inspectorate (Email: gif@gif.gov.pl; Website: www.gif.gov.pl) and Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Website: www.urpl.gov.pl)

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Final Analyses and Reporting

The survey will be registered in EU PAS register (currently the ENCePP e-register of studies). A survey report including the results of the 5 countries will be written in English, using a template which is based on the template included in the GVP module VIII and following STROBE recommendations in MS Word format. An abstract of the study results will be also entered into the ENCePP database.

12.2 Publications

Study findings will be considered for publication as open access. Any publication will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE).

IQVIA will develop the manuscript which describes the study design, main results, and conclusions of the study. This should be suitable for submission to a peer-reviewed medical journal. The manuscript will include the following standard disclaimer: “This document

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

expresses the opinion of the authors of the paper, and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties."

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

13. REFERENCES

1. Koźmiński P, Halik PK, Chesori R, Gniazdowska E. Overview of Dual-Acting Drug Methotrexate in Different Neurological Diseases, Autoimmune Pathologies and Cancers. International journal of molecular sciences. 2020;21(10).
2. Farber S. Some observations on the effect of folic acid antagonists on acute leukaemia and other forms of incurable cancer. Blood. 1949;4(2):160-7.
3. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. The New England journal of medicine. 1995;332(14):901-6.
4. Crews KR, Liu T, Rodriguez-Galindo C, Tan M, Meyer WH, Panetta JC, et al. High-dose methotrexate pharmacokinetics and outcome of children and young adults with osteosarcoma. Cancer. 2004;100(8):1724-33.
5. FDA. Methotrexate Injection, USP FDA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/011719s125lbl.pdf.
6. FDA. Prescribing Information XATMEP. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208004s002lbl.pdf.
7. Frei E, 3rd, Jaffe N, Tattersall MH, Pitman S, Parker L. New approaches to cancer chemotherapy with methotrexate. The New England journal of medicine. 1975;292(16):846-51.
8. Natale RB, Yagoda A, Watson RC, Whitmore WF, Blumenreich M, Braun DW, Jr. Methotrexate: an active drug in bladder cancer. Cancer. 1981;47(6):1246-50.
9. Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. Pharmacological reviews. 2005;57(2):163-72.
10. Goodkin DE, Rudick RA, VanderBrug Medendorp S, Daughtry MM, Schwetz KM, Fischer J, et al. Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. Annals of neurology. 1995;37(1):30-40.
11. Jacobs JW. Optimal use of non-biologic therapy in the treatment of rheumatoid arthritis. Rheumatology (Oxford, England). 2012;51 Suppl 4:iv3-8.
12. Karaahmet OZ, Bal A, Dulgeroglu D, Bahceci HK, Cakcı A. Methotrexate treatment in myasthenia gravis. Journal of clinical neuromuscular disease. 2014;16(2):106-7.
13. Lémann M, Zenjari T, Bouhnik Y, Cosnes J, Mesnard B, Rambaud JC, et al. Methotrexate in Crohn's disease: long-term efficacy and toxicity. The American journal of gastroenterology. 2000;95(7):1730-4.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

14. Roenigk HH, Jr., Auerbach R, Maibach HI, Weinstein GD. Methotrexate in psoriasis: revised guidelines. Journal of the American Academy of Dermatology. 1988;19(1 Pt 1):145-56.

15. Tugwell P, Bennett K, Gent M. Methotrexate in rheumatoid arthritis. Indications, contraindications, efficacy, and safety. Annals of internal medicine. 1987;107(3):358-66.

16. Baggott JE, Vaughn WH, Hudson BB. Inhibition of 5-aminoimidazole-4-carboxamide ribotide transformylase, adenosine deaminase and 5'-adenylate deaminase by polyglutamates of methotrexate and oxidised folates and by 5-aminoimidazole-4-carboxamide riboside and ribotide. The Biochemical journal. 1986;236(1):193-200.

17. FDA. Prescribing Information RASUVO. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205776s002lbl.pdf.

18. FDA. Prescribing Information OTREXUP PFS. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204824s009lbl.pdf.

19. Inoue K, Yuasa H. Molecular basis for pharmacokinetics and pharmacodynamics of methotrexate in rheumatoid arthritis therapy. Drug metabolism and pharmacokinetics. 2014;29(1):12-9.

20. FDA. Drugs@FDA:FDA-Approved drugs. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=008085.

21. Weinstein A, Marlowe S, Korn J, Farouhar F. Low-dose methotrexate treatment of rheumatoid arthritis. Long-term observations. The American journal of medicine. 1985;79(3):331-7.

22. Williams HJ, Willkens RF, Samuelson CO, Jr., Alarcón GS, Guttadauria M, Yarboro C, et al. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial. Arthritis and rheumatism. 1985;28(7):721-30.

23. Karami F, Ranjbar S, Ghasemi Y, Negahdaripour M. Analytical methodologies for determination of methotrexate and its metabolites in pharmaceutical, biological and environmental samples. Journal of pharmaceutical analysis. 2019;9(6):373-91.

24. Menting SP, Dekker PM, Limpens J, Hooft L, Spuls PI. Methotrexate Dosing Regimen for Plaque-type Psoriasis: A Systematic Review of the Use of Test-dose, Start-dose, Dosing Scheme, Dose Adjustments, Maximum Dose and Folic Acid Supplementation. Acta dermato-venereologica. 2016;96(1):23-8.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

25. Pradhan S, Sirka CS, Rout AN, Dash G, Sahu K. Acute Methotrexate Toxicity Due to Overdosing in Psoriasis: A Series of Seven Cases. Indian dermatology online journal. 2019;10(1):64-8.

26. Furst DE, Koehnke R, Burmeister LF, Kohler J, Cargill I. Increasing methotrexate effect with increasing dose in the treatment of resistant rheumatoid arthritis. The Journal of rheumatology. 1989;16(3):313-20.

27. Weinblatt ME. Methotrexate in rheumatoid arthritis: a quarter century of development. Transactions of the American Clinical and Climatological Association. 2013;124:16-25.

28. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying anti-rheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis care & research. 2012;64(5):625-39.

29. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe D, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease-modifying anti-rheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis. BMJ (Clinical research ed). 2016;353:i1777.

30. Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, et al. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). Annals of the rheumatic diseases. 2016;75(11):1917-23.

31. Khan ZA, Tripathi R, Mishra B. Methotrexate: a detailed review on drug delivery and clinical aspects. Expert opinion on drug delivery. 2012;9(2):151-69.

32. Morgan SL, Baggott JE, Vaughn WH, Austin JS, Veitch TA, Lee JY, et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. Annals of internal medicine. 1994;121(11):833-41.

33. IQVIA. OneKey by IQVIA-Healthcare Professionals Data. Available from: https://www.onekeydata.com/onekey/healthcare-professionals-data.

34. Covid-19 testing, Available from: https://www.m3global.com/dlc/M3OriginalResearch_COVID-19_Testing_HCPs.pdf

35. The Effect of COVID-19 on Healthcare Market Research Participation: Feasibility; Available at https://www.m3global.com/dlc/M3OriginalResearch_Effect_of_COVID-19_in_MR.pdf

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

36. COVID-19 TESTING: Patient Perspectives; available at: https://www.m3global.com/dlc/M3OriginalResearch_COVID-19_Testing_Patients_FINAL.pdf

37. Kish L. Survey Sampling. 1965. New York: JohnWileyand Sons.

38. Curtin R, Presser S, Singer E. Changes in Telephone Survey Nonresponse over the Past Quarter Century. The Public Opinion Quarterly. 2005;69(1):87-98.

39. Holbrook AL, Krosnick JA, Pfent A. The Causes and Consequences of Response Rates in Surveys by the News Media and Government Contractor Survey Research Firms. Advances in Telephone Survey Methodology. 2007;499-528.

40. Kellerman SE, Herold J. Physician response to surveys. A review of the literature. Am J Prev Med. 2001;20(1):61-7.

41. VanGeest JB, Johnson TP, Welch VL. Methodologies for improving response rates in surveys of physicians: a systematic review. Eval Health Prof. 2007;30(4):303-21.

42. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.

43. Wyatt JC. When to use web-based surveys. J Am Med Inform Assoc. 2000;7(4):426-9.

44. Nederhof AJ. Methods of coping with social desirability bias: A review. European Journal of Social Psychology. 1985;15(3):263-80.

45. EphMRA. EphMRA. Code of Conduct 2013. Available from: https://www.ephmra.org/standards/code-of-conduct-aer/.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

1	Prescriber questionnaire
2	Pharmacist questionnaire
3	Patient questionnaire

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

ANNEX 2. LIST OF HEALTHCARE PROFESSIONALS

	Country	List of specialties
1	**Germany**	The educational material(s) was sent to the following: • General Practitioners • Internists (without specialisation) • Internists with specialisation Haematology/Oncology • Internists with specialisation Gastroenterology • Physicians with additional accreditation Rheumatology • Dermatologists • Paediatrists • Physicians with additional accreditation - Geriatrics • Community pharmacies and hospital pharmacies • “Stufenplanbeteiligte” and company addresses • German Association of General Practitioners • Professional Society of Rheumatology (RheumatologischeFachgesellschaft DGRH) • German Society of Dermatology (Deutsche Dermatologische Gesellschaft e.V.) • German Society for Haematology and Oncology (DGHO – Deutsche Gesellschaft für Hämatologie und Onkologie) • German Society for Oncology (DGO – Deutsche Gesellschaft für Onkologie) • German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS – Deutsche Gesellschaft für Gastroenterologie, Verdauungs-u. Stoffwechselkrankheiten) • German Society for Geriatrics (Deutsche Gesellschaft für Geriatrie e.V.) • German Society for Internal Medicine (Deutsche Gesellschaft für Innere Medizin e.V.) • German Society for Child and Adolescent Medicine (Deutsche Gesellschaft für Kinder- und Jugendmedizin) • German Society for medical rehabilitation (Deutsche Gesellschaft für Medizinische Rehabilitation e.V.(DEGEMED)) The DHPC was sent to the following : • General Practitioners • Rheumatologists • Dermatologists • Oncologists • Gastroenterologists • Geriatricians • Internists • Paediatricians • Community pharmacies and hospital pharmacies • German Association of General Practitioners

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

		• Professional Society of Rheumatology (Rheumatologische Fachgesellschaft DGRH) • German Society of Dermatology (Deutsche Dermatologische Gesellschaft e.V.) • German Society for Haematology and Oncology (DGHO – Deutsche Gesellschaft für Hämatologie und Onkologie) • German Society for Oncology (DGO – Deutsche Gesellschaft für Onkologie) • German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS – Deutsche Gesellschaft für Gastroenterologie, Verdauungs-u. Stoffwechselkrankheiten) • German Society for Geriatrics (Deutsche Gesellschaft für Geriatrie e.V.) • German Society for Internal Medicine (Deutsche Gesellschaft für Innere Medizin e.V.) • German Society for Child and Adolescent Medicine (Deutsche Gesellschaft für Kinder- und Jugendmedizin)
2	**France**	The educational material(s) and DHPC were sent to the following: • Rheumatologists • Dermatologists • General practitioners • Oncologists • Internists • Emergency physicians • Dispensary pharmacists • Hospital pharmacists • Private nurses • Directors of Care • Nursing staff • Directors of Establishments for Dependent elderly People (EHPAD)
3	**Greece**	The educational material(s) and DHPC were sent to the following: • Rheumatologists • Dermatologists • Paediatricians • Gastroenterologists • Haematologists • General Practitioners • Internists and pharmacists of both private and hospital sectors and relevant scientific societies
4	**Poland**	The educational material(s) and DHPC were sent to the following: • Oncologists • Haematologists • Rheumatologists • General Practitioners • Internists • National and provincial consultants of the different specialisations i.e. oncological, haematological, rheumatological, of internal medicine

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

5	**Sweden**	The educational material(s) was sent to the following: • Rheumatologists • Dermatologists • Haematologists • Paediatrician • Hospital pharmacists, including head of departments for the specified clinics and also Head of department at medicine clinics at the hospitals The DHPC was sent to the following: • Rheumatologists • Dermatologists • Gastroenterologists • Paediatric rheumatologists and chief physician/Head of paediatric clinics and chief physician/Head of medicine clinics

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

ANNEX 3. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Impact of EU label changes for medicinal products containing methotrexate for weekly administration: risk awareness and adherence, A survey study
EU PAS Register® number: TBD **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	☒	☐	☐	6

[4] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.2 End of data collection[5]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	

[5] Date from which the analytical dataset is completely available.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☐	☐	☐	
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2, 9.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9.1
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.1

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
	9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☐	☐	☒	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section number**
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8.2

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9.1
12.1.2 Information bias?	☒	☐	☐	9.9.1
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	10.3

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section number**
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.3
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol:	Leila Karimi
Date:	17 December
Signature:	

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

ANNEX 4. SUMMARY OF QUALITATIVE INTERVIEWS

4.1 Physicians

	Concept	Doctor 1 [Dermatologist-Germany]	Doctor 2 [Rheumatologist-Sweden]	Doctor 3 [GP- Germany]
1.	**Indications for which the doctor prescribes once-weekly methotrexate**	Psoriasis	Different rheumatological diseases – rheumatoid arthritis, psoriatic arthritis etc.	All listed indications: • psoriasis • rheumatoid arthritis • psoriatic arthritis • ulcerative colitis • Crohn's disease • dermatitis
2.	**Years of experience**	Around 10 years	Around 15 years	22 years
3.	**Setting**	Primary and secondary care (2 jobs); main is primary care	University hospital; mainly outpatients	Private medical office; rural setting
4.	**Most common route patients take before they arrive to the doctor**	• Different; usually they come from family doctor • However, nowadays more and more patients are coming directly to her	• Primarily via primary healthcare unit like GPs, family doctor • Sometimes, referred from dermatologists, infectious disease specialists	• Most patients come directly due to the rural setting (70%); and the rest from specialists/hospitals (30%) mostly internists • Other specialists located too far away • He has received dermatology training from the military, so he does not need to rely on specialists for psoriatic arthritis; however, if he encounters problems he refers patients to

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Doctor 1 [Dermatologist-Germany]	Doctor 2 [Rheumatologist-Sweden]	Doctor 3 [GP- Germany]
				another dermatologist or the dermatology station of the military hospital • Many of the patients he sees especially RA/psoriatic arthritis have been under his care for several years and are being treated with MTX successfully
5.	**Case-load of patients who are prescribed once-weekly methotrexate**	• 5 patients per month; 1 patient per month is new • Patients visit per month (for blood tests etc.); more frequently initially (maybe once a week)	• Approximately 25 patients in a week; 2-3 new patients • Patients visit every 3-6 months depending on whether case is new or old	• Around 20 in a month • New patients decreasing as he prefers switching to biologicals • Patients used to visit weekly to receive infusions (pre-COVID); now he contacts them mostly via telephone on a monthly basis
6.	**Role of the doctor in managing patients prescribed with once-weekly methotrexate**	All aspects - Diagnosis; initiates treatment if other therapies have failed and there are no contraindications then she prescribes MTX; treatment and treatment management – blood results, dosing, changing treatment if therapy not working	All aspects - diagnosis; treatment; treatment management	All aspects - diagnosis; treatment; treatment management (due to rural setting)
7.	**Details about the initiation/renewal of once-weekly methotrexate**	• If local therapies are not working, too much body surface area affected, systemic therapies are warranted to treat disease • Depending on patient willingness, compliance etc. she prescribes injections or oral MTX (sometimes in parallel with another systemic therapy)	• Initiates MTX at diagnosis; 95% patients • Prefers to prescribe oral MTX • If it is a new case, he prescribes for 3 months till they come back; longer prescription for older cases • He is the one who renews the prescription • Patient gets MTX from any pharmacy	• Prescription depending on the disease severity – 2 months, 4 months, 6 weeks etc. • Prescribes based on disease/treatment history and previous MTX experience, does not prescribe MTX as first-line therapy • He used to perform infusions (pre-COVID); now prefers to prescribe oral MTX (90% vs. 30% earlier)

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Doctor 1 [Dermatologist-Germany]	Doctor 2 [Rheumatologist-Sweden]	Doctor 3 [GP- Germany]
		• Prescribes mostly self-injection (5 injections in a pack) as they work better • She is the one who renews the prescription; initially smaller packs, but later bigger packs (12 injections in a pack) to reduce costs to the patient; however, patient visits monthly for tests etc. • Patient gets MTX from any community pharmacy (however, pharmacies need to order it)		• Constantly monitors for side effects and stops MTX as required • Patient gets MTX from any pharmacy
8.	**Patient guidance provided by the doctor during treatment with once-weekly methotrexate**	• Explains to the patient about the treatment, blood tests, visits etc. who in her opinion are intelligent enough to understand • Makes sure patients understand, and asks them to explain the information back to her, if they cannot she does not prescribe MTX, and prescribes some other therapy (15-20% patients) • Sometimes, if required, suggests patients google additional information	• At initiation, he advices patients on once-weekly dosing, alcohol consumption, subjective side effects like headaches, nausea etc. • At subsequent visits, he checks if patients are taking MTX correctly • Provides patient leaflet with general information • 3-4 years ago, nurses used to provide advice, but that has stopped now	He is very involved in the treatment and management plan of his patients, and ensures frequent visits/calls to address any issues
9.	**Details on experience with methods/tools/advice to ensure patient**	• She tells the patient to choose a day to take MTX, e.g. Sunday • Does not know how patients set reminders • Cases from colleagues – patient did not understand the doctor correctly, came	• He does not recommend specific day of the week, patients decide themselves • Does not know any patients who have taken incorrect dose • Does not know how patients set reminders	• He is aware of the new rule that the day of the week needs to be written down by the medical doctor; the pharmacist needs to write on the box

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Doctor 1 [Dermatologist-Germany]	Doctor 2 [Rheumatologist-Sweden]	Doctor 3 [GP- Germany]
	adherence to once-weekly methotrexate	again and asked for more medication even though he should have had enough, that is when the doctor realised that the patient had taken the oral dose daily, the doctor explained again and continued with the same treatment; however, she mostly prescribes injections, very rarely oral MTX		• Does not have issues with patient compliance (expects a monthly call from the patient to discuss side effects and compliance)
10.	**Information on methotrexate patient card**	Never saw the card with patient/does not provide	Never saw the card with patient/does not provide; does not think patients receive MTX patient card	Patients have not received the patient card; they also do not prefer this mode; prefer the instructions on the prescription/box
11.	**Information on any educational material related to once-weekly methotrexate**	General - Websites like Medscape etc., newsletters	• Has received MTX leaflets from pharmaceutical companies, usually for injections Mentions not many updates as MTX is an old medication, information about it is well established	• Before COVID, has received MTX document from a pharmaceutical company to help guide patients after an office visit • Has telephone number of some pharmaceutical reps, online portals, DocCheck etc.
12.	**Challenges/ Concluding remarks**	• One patient was unable to self-inject, so she prescribed oral • Sometimes, liver problems Overall, the treatment generally works well; however, its associated with side effects, frequent blood tests, patient monitoring etc. compared to other medications; MTX is	• Side effects which require dose changes • Treatment initiation complicated by lung issues like fibrosis • Overall, considers it as a good standard first-line treatment	• Recommends pharmaceutical companies create podcasts, webinars etc. via DocCheck for German doctors to stay informed on therapies

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Doctor 1 [Dermatologist-Germany]	Doctor 2 [Rheumatologist-Sweden]	Doctor 3 [GP- Germany]
		starting to be replaced with biologicals as first-line treatment in recent times		

4.1 Pharmacists

	Concept	Pharmacist 1 [Germany]	Pharmacist 2 [Germany]	Pharmacist 3 [Sweden]
1.	**Indications for which the pharmacist dispenses once-weekly methotrexate**	Mostly RA; does not always know the diagnosis as the prescription does not have details, only if the patients inform him	RA, psoriatic arthritis, psoriasis	All of mentioned diseases in the list • psoriasis • rheumatoid arthritis • psoriatic arthritis • ulcerative colitis • Crohn's disease • dermatitis
2.	**Years of experience**	12 years	13 years	10 years
3.	**Pharmacy setting**	Community pharmacy	Community pharmacy	Pharmacy situated in a shopping mall
4.	**Common physician specialties that prescribe once-weekly methotrexate**	• Mostly specialists like rheumatologists, also oncologists; always from a specialist • Less often GPs	• Mostly specialists like rheumatologists (75%), also dermatologists etc. (both initial and follow-up prescriptions) • Less often GPs (25%) – only follow-up prescriptions	• Mostly different specialists like internal medicine, dermatologists, inflammatory disease specialists etc. • Less often GPs

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Pharmacist 1 [Germany]	Pharmacist 2 [Germany]	Pharmacist 3 [Sweden]
	in the pharmacist's experience			
5.	**Case-load of patients who are dispensed once-weekly methotrexate**	• 4 patients per month; mix of new/old, most are coming for renewals	• 25 patients per week • 15 patients are new and 10 are for renewals • Frequency of visit depends on package size i.e. when the patient runs out of the medication; mostly 12 weeks	• 7 patients per week • Frequency – approximately every 3 months • Mentioned that MTX not prescribed much nowadays
6.	**Prescription details of once-weekly methotrexate**	• Prescriptions usually for 3 months • 50:50 – tablets/injections • Prescription does not have the specific day marked • Product needs to be ordered	• Prescriptions usually for 3 months • Mostly injections (80%); oral (20%) • Sometimes, prescription has the specific day marked	• Prescriptions usually for 1 year; however, patients get product for only a limited number of months • Mostly injections • Only electronic prescriptions in Sweden sent by the doctor; "pharmacy etiquette" on package, can have specific day marked by doctor, who writes how to take the medicine after talking to patient; prints the "pharmacy etiquette" which is then glued onto the package
7.	**Patient guidance provided by the pharmacist during treatment with once-weekly methotrexate**	• Asks if patients know how to use it, then provides them information and/or how to look online for pictures and videos • Patients generally know the information from their doctors, he mostly repeats the advice	• He/assistant provides relevant information only after asking patients if they require any advice, depending on patient's experience with the medication • Checks if patients are experienced in using injectable; discusses if have they attended a training – to learn dosing instructions, route, site, how to administer, provided with leaflets etc.	• She confirms if the patient knows how/when to take the medicine and any details written down by the physician • Answers any questions the patients might have regarding side effects, interactions etc.; common patient questions include side effects, reassurance about dosage schedule • Generally (not MTX specifically), nurses/doctors can conduct trainings

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Pharmacist 1 [Germany]	Pharmacist 2 [Germany]	Pharmacist 3 [Sweden]
			*Trainings organised in peer groups by pharmaceuticals companies, and usually conducted by nurses; 60% doctors and 40% pharmacists suggest patients attend these trainings, depending on availability	
8.	**Details on experience with methods/tools/advice to ensure patient adherence to once-weekly methotrexate**	• Knows patients who use the mobile calendar function • Suggests that maybe for some patients' apps might be beneficial • Does not know any patients who have taken incorrect dose	• Knows patients who use mobile based reminders • Suggests that maybe for some patients' apps might be beneficial e.g. diabetes related apps which send reminders • Not a big supporter of apps; instead advices to attend trainings, listen to HCP advice, talk to peers etc. • Does not know any patients who have taken incorrect dose	• Recommends dosettes, writing on package, setting alarms • Can add in more instructions if needed on the prescription • Does not know any patients who have taken incorrect dose; rarely they forget the dose
9.	**Information on methotrexate patient card**	Mentioned that years ago there was a flyer; does not remember clearly; has not seen patient card with any patient or product (mentions might be inside the package)	• Mentioned a card related to MTX which has personal details, physician contact information, therapy details, blood readings, striking events like side effects etc. i.e. any information subsequent physicians might need; card received from the prescribing physician Post interview finding: Not patient card, but monitoring form	Has not seen patient card with any patient or product.

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Pharmacist 1 [Germany]	Pharmacist 2 [Germany]	Pharmacist 3 [Sweden]
10.	**Information on methotrexate product packaging**	• Sometimes, he writes on the package with a small sticker – special day of intake e.g. every Tuesday, dosage e.g. once a week etc. depending on what the patient requests • Has not noticed any update on the packaging; manufacturers usually mention for e.g. once-weekly dosage on package; if it is not mentioned he writes it • Considers outer packaging useful; he or his assistant talks about it with the patients, he knows his colleagues also discuss this with their patients	• Not noticed any open space/reminder to mark day on packaging; however, a clear remark - once-weekly present on packaging • Has read that outer packaging will be updated from a pharmaceutical newspaper; possibility that it will include day of administration; he has a lot of old stock might see it once he gets new stock • Considers packaging instructions useful	• Mentioned there might be a blister package inside, but she does not open it; checks how the tablet looks like/instruction to divide dose from FASS.se • Oral tablets are usually in a container with a lid; does not mention any specific day • Not aware of any updates
11.	**Information on any educational material related to once-weekly methotrexate**	• General - Pharmaceutical newspapers, internet, manufacturer website, information from pharma meetings out of office • No MTX related update received from any regulatory agency	• General - Pharmaceutical liaisons/representatives	• General – finding information herself • No MTX related update received from any regulatory agency • Would be helpful to get guide from pharmaceutical companies
12.	**Challenges/ Concluding remarks**	• Very rarely, product issues like device malfunction – only one time encountered a patient who was unable to press down on the injection Overall, no issues with the medication	• Some differing patient preferences regarding oral vs injectables • Side effects, which make the patients refrain from MTX • In Germany, sometimes the drug is not available on time – due to COVID-19, bureaucratic issues, supply chain; gap can be 1-2 weeks; his pharmacy upscales the supply but other pharmacies that do not face issues	• Overall, no issues with the medication

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Pharmacist 1 [Germany]	Pharmacist 2 [Germany]	Pharmacist 3 [Sweden]
			• Overall, no issues with the medication except for delivery issues	

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

4.3 Patients

	Concept	Patient 1 [Germany]	Patient 2 [Germany]	Patient 3 [France]
1.	**Age/ Employment status/ Marital status**	70 years/ Retired for 21 years/ Married	60 years/ Employed	79 years
2.	**Indication for which the patient is prescribed once-weekly methotrexate**	Crohn's disease and parallel with the other drugs as a combination for rheumatoid arthritis	Psoriasis	Psoriatic arthritis
3.	**Time since diagnosis of indication for which the patient is prescribed once-weekly methotrexate**	Initially diagnosed as ulcerative colitis, however 20 years ago diagnosis was updated to Crohn's disease. RA was diagnosed 35 years ago.	Initially diagnosed as ulcerative colitis, however 20 years ago diagnosis was updated to Crohn's disease. RA was diagnosed 35 years ago.	Diagnosed in 1999; was initially prescribed other therapies
4.	**Time since initiation of once-weekly methotrexate**	As a base, he took Humira, which is not being processed anymore. So, there was the question if he should be taking MTX in addition to that, or if he should try a new basic drug. And the alternative he agreed to was to take MTX in addition, and it had a positive effect after about 3-4 weeks. MTX (as additional therapy) started February 2021	• Has been taking MTX for around 10 years Although, he has heard that MTX should not be taken for a long duration at high doses due to the side effects, he has not been able to do so as he develops rheumatic problems	• Has been taking MTX since 2011 Although, he has heard that MTX should not be taken for a long duration at high doses due to the side effects, he has not been able to do so as he develops rheumatic problems

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Patient 1 [Germany]	Patient 2 [Germany]	Patient 3 [France]
5.	**Speciality of physician who prescribed once-weekly methotrexate**	Rheumatologist	Dermatologist/Rheumatologist	Rheumatologist
6.	**Methotrexate initiation/renewal/treatment plan**	• Once-weekly injection • He was prescribed MTX after reassurance from doctor, since he was sceptical as had gotten shingles the first time • Blood, liver and kidney tests: At treatment initiation, weekly for 4 weeks, and then it changed to 3 times at a fortnightly rhythm, and now only every 3 months. And now, the rheumatologist does them as well • Takes MTX on Fridays, on Sundays takes the folic acid accordingly, and injects Humira on Monday	• Once-weekly oral tablet: in the process of a dose reduction (from 30mg to 25mg, and now trying 20mg since 3 weeks) • He was prescribed MTX by a dermatologist after suffering with aggressive psoriasis for a long time; had undergone radiotherapy etc. which did not treat the condition • Currently, he is being treated by a rheumatologist who is continuing the prescription • Visits doctor every 3 months; blood tests performed at every visit • Takes MTX on Sunday evenings, followed by folic acid a day later	• He was prescribed MTX by a rheumatologist who is still his doctor • He initially resisted starting MTX as he had heard of breathing issues from a friend while hiking, however he gave in when his feet/fingers started getting deformed • Visits doctor every 3 months; blood tests performed at every visit • Alternates between 4 tablets and 3 tablets of Methotrexate once a week, taken on Mondays; Forsine on Wednesdays to counter the side effects of the Methotrexate (he had suggested the alternating plan to the doctor instead of her)
7.	**Prescription details**	• Picked up from chemist • Prescription for 12 injections, i.e. 12 weeks • Renewed every 3 months after doctor visit	• Picked up from chemist • Renewed every 3 months after doctor visit • Mentions that he is on MTX when being prescribed other medications by other doctors (not suggested by his doctor; he informs them based on his own decision)	• Picked up from chemist • Renewed every year; picks up medication monthly

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Patient 1 [Germany]	Patient 2 [Germany]	Patient 3 [France]
8.	**Patient guidance provided by the doctor/pharmacist during treatment with once-weekly methotrexate**	• Prescriber informed him about MTX's successful background as first-line therapy for his indication • As he had the experience with injecting Humira, the patient was confident on how to use MTX – told the prescriber that a lengthy explanation was not required • Pharmacist: No, as received all details from rheumatologist	• Pharmacist always asks about concomitant medication; this is why he prefers this pharmacy, as the pharmacist is very knowledgeable on drug interactions; also, explains on how to take the medicine each time he picks up a prescription	• Although doctor tried to tell him about the risks, he prefers not to know • Also mentions that the doctor was not very communicative initially, but now they have a good relationship and she answers any questions that he might have • Rheumatologist initially provided details on posology; no advice from pharmacist
9.	**Concerns about once-weekly methotrexate**	• Whether it would trigger another episode of shingles	• Thinks it might be linked to his increased levels of cholesterol and kidney issues, although doctors have not confirmed the causal relationship; mentions it could be age-related	• Mentions he experienced hair loss, lost a tooth, loss of sexual libido within 3-4 years of starting MTX; thinks it could be linked to MTX use
10.	**Details on experience with methods/tools/advice to ensure adherence to once-weekly methotrexate**	• Days written by hand by him on his medication plan (printed out by the doctor), which he keeps in handbag along with other medical cards like the vaccination card as a part of an "emergency set" • Secondly, this procedure is so engrained in his head, it is simply part of my life, the same way the physiotherapy appointments are part of it, so is this. I do not need to write this down especially.	• Does not need reminders to remember taking MTX on correct day	• Has a weekly pill organiser, and always fills it up on Thursdays; takes MTX on Mondays, the other medications on Thursdays, and this way knows on Thursdays how many pills he has taken. It prevents him from making mistakes and helps him take 4 MTX tablets each time; considers it as the most practical solution

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Patient 1 [Germany]	Patient 2 [Germany]	Patient 3 [France]
11.	**Information on methotrexate patient card**	• Never saw the card • Believes it would be useful similar to the patient card for blood thinners he uses • Thinks if it was only little credit-card sized patient cards, that would be too small; A4 sized cards like the medication plan that he has printed out and folded would be better • When he has his next appointment in October, he intends to ask the rheumatologist about it; however, thinks the doctor will tell him it does not exist	• Never saw the card • Believes it would be useful if it contained information on drug interaction, what to do in case of emergencies like hospitalisations • Mentions if he knew something like the patient card existed, he would have asked his doctor	• Never saw the card • Believes it would not be useful as it would lead to excessive worrying; the patient information leaflet (PIL) already has enough information
12.	**Information on any educational material related to once-weekly methotrexate**	Prefers to rely on doctor advice, although aware of the PIL he does not use it. Believes reading additional information will lead to excessive and unnecessary worrying.	Although aware of the PIL that was provided initially by the dermatologist to help him make the decision if he wanted to start MTX (chose MTX as the advantages were more than disadvantages), he prefers not to know about all the side effects; believes reading additional information will lead to excessive and unnecessary worrying.	• Looked up only general information online; believes reading additional information will lead to excessive and unnecessary worrying Aware of the boxed warning, but found it too complex; did not ask the doctor/pharmacist for clarification
13.	**Challenges/Concluding remarks**	• Has had a positive experience because unlike cortisone, MTX has helped reduce the swelling in his right hand; hand has become more mobile	• He like MTX as it has helped to bring his psoriasis completely under control (except for minor joint problems) that has improved his life dramatically • He finds it easy to use	• He likes MTX as he tolerates it well

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Concept	Patient 1 [Germany]	Patient 2 [Germany]	Patient 3 [France]
		• Finds the injections are easy to handle • The box is easy to open, it is well organised inside, it is all together, the swab and the syringe • At the moment, no concerns, and does not expect any in the future • Good explanation provided by doctor		

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

ANNEX 5. ASSESSMENT OF SUCCESS

5.1 Assessment of Success (Prescriber questionnaire)

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctly answered question	Assessment of success
Receipt and Awareness (5 questions)	Q1. Please select the option that best describes your experience with the *[Direct Healthcare Professional Communication (DHPC): country-specific name]* distributed on *[country-specific date of distribution]* for methotrexate formulations?	Yes	Question completed correctly [Answer '1' or '2' is desirable]	A prescriber is successful for **receipt and awareness** when he/she receives the DHPC, the HCP guide, the HCP checklist (desirable answers) and is aware of the patient card (desirable answers). Success for receipt and awareness if ≥80% of prescribers are successful
	Q2. Please select the option that best describes your experience with the *[HCP guide: country-specific name]* distributed on *[country-specific date of distribution]*?	Yes	Question completed correctly [Answer '1' or '2' is desirable]	
	Q3. Please select the option that best describes your experience with the *[HCP checklist: country-specific name]* distributed on *[country-specific date of distribution]*?	Yes	Question completed correctly [Answer '1' or '2' is desirable]	
	Q4. Please select the option that best describes your experience with the *[patient card: name in the local language]* (for oral methotrexate formulations)?	Yes	Question completed correctly [Answer '1' or '2' or '3' is desirable]	

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctly answered question	Assessment of success
	Q5. In your daily practice, what version of the educational materials (EM) related to methotrexate do you use?	No; complementary information on mode of distribution		
Knowledge (1 question)	Q6. According to your knowledge about the conditions of use for methotrexate, please indicate if you agree or disagree with the following statements.	Yes	Question completed correctly (16 sub-questions [10 False and 6 True])	A prescriber is successful for **knowledge** when he/she scores at least 13 out of 16 points (80%) for sub-questions that are correctly answered. Success for knowledge if ≥ 80% of prescribers are successful.
Self-declared behaviour (7 questions)	Q7. What helps you make treatment decisions while managing patients who have been prescribed, oral and parenteral, once-weekly methotrexate?	No; complementray information on making treatment decisions		A prescriber is successful for **self-declared behaviour** when all questions regarding self-declared behaviour are completed with desirable answers. Success for self-declared behaviour if ≥80% of prescribers are successful.
	Q8. How would you describe your experience with the *[HCP guide: country-specific name]*?	No; complementary information on user friendliness of educational material		
	Q9. How would you describe your experience with the *[HCP checklist: country-specific name]*?	No; complementary information on user		

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctly answered question	Assessment of success
		friendliness of educational material		
	Q10. How often do you provide dosing instructions and information about overdose symptoms for once-weekly, oral and parenteral, methotrexate to the patient/caregiver?	Yes	Question completed correctly [Answer '1' is desirable]	
	Q11. Please specify the reasons you choose to not inform the patient/caregiver about the dosing instructions and symptoms of overdose at each/any visit?	No; complementary information on reason for self-declared behaviour to Q10		
	Q12. How do you write down the day of the week the patient should take the once weekly dose of methotrexate, oral and parenteral, in the prescription?	Yes	Question completed correctly [Answer '1' is desirable]	
	Q13. Please specify the reasons you do not write the day of intake in the prescription at each/any visit?	No; complementary information on reason for self-declared behaviour to Q12		

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

5.2 Assessment of Success (Pharmacist questionnaire)

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctly answered question	Assessment of success
Awareness (3 questions)	Q1. Please select the option that best describes your experience with the *[patient card: name in the local language]* (for oral methotrexate formulations)?	Yes	Question completed correctly [Answer '2'is desirable]	A pharmacist is successful for **awareness** when he/she is aware of the patient card and the visual reminder on MTX outer packaging (desirable answers). Success for awareness if ≥80% of pharmacists are successful
	Q2. In your daily practice, what version of the *[patient card: name in the local language]* related to methotrexate are you aware of?	No; complementary information related to Q1		
	Q3. Please select the option that best describes your experience with the methotrexate outer packaging	Yes	Question completed correctly [Answer '1'is desirable]	
Knowledge (5 questions)	Q4. According to your knowledge about the *[patient card: name in the local language]*, please indicate if you agree or disagree with the following statements	Yes	Question completed correctly [6 sub-questions; answers '1', '3' and '5' are True; '2', '4' and '6' are False]	A pharmacist is successful for **knowledge** when he/she scores at least 8 out of 10 points (80%) for sub-questions that are correctely answered. Success for knowledge if ≥ 80% of pharmacists are successful.
	Q5. According to your knowledge about the safety measures on the outer packaging of oral and parenteral methotrexate-containing products, please indicate if you agree or disagree with the following statements	Yes	Question completed correctly [4 sub-questions; answers '1' and '3' are True; '2' '4' and '5' are False]	
	Q6. What is your experience with the *[patient card: name in the local language]*?	No; complementary information on user friendliness of patient card		

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctly answered question	Assessment of success
	Q7. Please specify the reasons you do not find the *[patient card: name in the local language]* useful?	No; complementary information on user friendliness of patient card		
	Q8. Please specify the reasons you do not always choose to inform the patient/caregiver about the *[patient card: name in the local language]*?	No; complementary information regarding informing patients about the patient card		
Self-declared behaviour (2 questions)	Q9. Please select the option that best describes your experience with the outer packaging of methotrexate once weekly products	Yes	Question completed correctly [Answers '1' or '2' are desirable]	A pharmacist is successful for **self-declared behaviour** when the question regarding self-declared behaviour is completed with desirable answers. Success for self-declared behaviour if ≥80% of pharmacists are successful.
	Q10. Please specify the reasons you do not frequently/always mark the day of intake for once-weekly methotrexate prescriptions on the outer packaging (for oral formulations)?	No; complementary information related to Q8		

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

5.3 Assessment of Success (Patient questionnaire)

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctly answered question	Assessment of success
Receipt and Awareness (6 questions)	Q1. Please select the option that best describes your experience with the *[patient card: name in the local language]* (only for oral methotrexate formulations)?	Yes	Question completed correctly [Answer '1' or '2' is desirable]	A patient is successful for **awareness** when he/she receives the patient card, and is aware of the boxed warining in the packaging leaflet and visual reminder on the outer packaging (desirable answers). Success for awareness if ≥80% of patients are successful.
	Q2. How did you obtain the information regarding the existence of the *[patient card: name in the local language]* (only for oral formulations)?	No; complementary information on source of patient card		
	Q3. Please select the option that best describes your experience with the methotrexate package leaflet	Yes	Question completed correctly [Answer '1'is desirable]	
	Q4. How did you obtain the information regarding the existence of the boxed warning on the methotrexate package leaflet?	No; complementary information on source of package leaflet knowledge		
	Q5. Please select the option that best describes your experience with the methotrexate outer packaging of oral and parenteral methotrexate-containing products	Yes	Question completed correctly [Answer '1'is desirable]	

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Q6. How did you obtain the information regarding the existence of the visual reminder on when to use/take methotrexate?	No; complementary information on source of visual reminder on the outer packaging		
Knowledge (13 questions)	Q7. According to your knowledge about the purpose of the *[patient card: name in the local language]* (only for oral methotrexate formulations), please indicate if you agree or disagree with the following statements	Yes	Question completed correctly (6 sub-questions [3 False and 3 True])	A patient is successful for **knowledge** when he/she scores at least 20 out of 25 points (80%) for questions, including sub-questions, which are completed with correct/desiable answers. Success for knowledge if ≥ 80% of patients are successful.
	Q8. According to your knowledge about the safety measures on the outer packaging of oral and parenteral methotrexate-containing products, please indicate if you agree or disagree with the following statements	Yes	Question completed correctly (4 sub-questions [2 False and 2 True])	
	Q9. Did your pharmacist write the weekday for intake in the respective box of the reminder on the methotrexate packaging?	No; complementary information on packaging reminder		
	Q10. According to your knowledge about the conditions of use for methotrexate, please indicate if you agree or disagree with the following statements.	Yes	Question completed correctly (6 sub-questions [3 False and 3 True])	
	Q11. According to your knowledge about methotrexate, which of the following symptoms are associated with methotrexate overdose?	Yes	Question completed correctly (9 sub-questions [2 False and 7 True])	

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

	Q12. How did you gain an understanding about the dosing instructions for once weekly methotrexate?	No; complementary question on source of understanding about the dosing instructions		
	Q13. How did you gain an understanding about the risks (side-effects, risk of overdose etc.) associated with taking methotrexate?	No; complementary question on source of understanding about the risks		
	Q14. What helps you to remember to take methotrexate as a once-weekly dose?	No; complementary question on reminders set by patients		
	Q15. How would you describe your experience with the *[patient card: name in the local language]*?	No; complementary information on user friendliness of patient card		
	Q16. How would you describe your experience with the visual reminder for taking/using methotrexate/ noting down the day of the week to take methotrexate on the outer packaging?	No; complementary information on user friendliness of packaging		
	Q17. How would you describe your experience with the information provided in the boxed warning in the methotrexate package leaflet?	No; complementary information on user		

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

		friendliness of packaging		
	Q18. According to your experience please indicate if you have ever accidently taken the once-weekly dose of methotrexate as a daily dose	No; complementary question on patient experience		
	Q19. According to your experience please indicate for which reason(s) you took the once-weekly dose of methotrexate as a daily dose?	No; complementary question related to Q18		

Copyright © 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.