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Data analysis plan

Rapid Data Analysis – Systemic fluoroquinolones and thrombotic thrombocytopenic purpura (TTP)

Contact for data analysis

Contact mailbox	ICU@ema.europa.eu
Date	9 June 2021

Request

Affiliation	Norwegian Medicines Agency
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Background

Short title of topic	Systemic fluoroquinolones and thrombotic thrombocytopenic purpura (TTP)
Regulatory procedure	Signal procedure (EPITT no. 19669)
Background	<p>The signal originates from a review of case reports within EudraVigilance and signal detection based on disproportionality.</p> <p>The review identified 5 well documented literature reports of TTP for ciprofloxacin. The time to onset was <21 days (4 days, 5 days and 13 days). None of the patients had a history of malignancy or haematopoietic stem cell transplantation. Other known precipitating factors were also excluded.</p> <p>TTP is considered an ultraorphan disease with an incidence rate of 2.1 per million.</p> <p>TTP is listed in the USPI for Cipro®, and the SmPC for the innovator Ciproxin® lists several manifestations of TTP (thrombocytopenia, haemolytic anaemia, convulsions, and confusion).</p>

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

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Background

Description of research question

Is there evidence of an association between systemic fluoroquinolones and acquired TTP?

1. List of abbreviations

<i>MAH</i>	<i>Marketing Authorisation Holder</i>
<i>EMA</i>	<i>European Medicines Agency</i>
<i>PRAC</i>	<i>Pharmacovigilance Risk Assessment Committee</i>
<i>RDA</i>	<i>Rapid Data Analysis</i>

2. Rationale and background

Fluoroquinolone antibiotics act by inhibiting enzymes involved in bacterial DNA synthesis. Fluoroquinolones have been used since the 1980s as broad-spectrum antibiotics with low propensity for development of antibiotic resistance.

Immune-mediated thrombocytopenia is a known rare adverse reaction to fluoroquinolones [1-5]

Thrombotic thrombocytopenic purpura (TTP) is a rare disease that is associated with microangiopathy, haemolytic anaemia, thrombosis and thrombocytopenia. Although the exact cause of TTP is not known it is associated with a deficiency of the von Willebrand factor cleaving protease ADAMTS13, allowing large complexes of von Willebrand factor to circulate in the blood. TTP exists in a congenital form and in an acquired form. The acquired form is caused by antibody to ADAMTS13.

The signal originates from a review of case reports within EudraVigilance and signal detection based on disproportionality.

The review identified 5 well documented literature reports of TTP for ciprofloxacin. The time to onset was <21 days (4 days, 5 days and 13 days). None of the patients had a history of malignancy or haematopoietic stem cell transplantation. Other known precipitating factors were also excluded.

TTP is considered an ultraorphan disease with an incidence rate of 2.1 per million.

TTP is listed in the USPI for Cipro®, and the SmPC for the innovator Ciproxin® lists several manifestations of TTP (thrombocytopenia, haemolytic anaemia, convulsions, and confusion).

3. Research question and objectives

Is there evidence of an association between systemic fluoroquinolones and acquired TTP, i.e. is there an increased frequency of acquired TTP following treatment with fluoroquinolones?

4. Research methods

4.1. Study design

A descriptive comparative incident cohort design is proposed where the incidence of TTP in patients initiating systemic fluoroquinolone treatment is compared to broad spectrum penicillins. A separate analysis will compare patients initiating systemic fluoroquinolones to patients initiating azithromycin.

We will identify patients with a first prescription for either a systemic fluoroquinolone or a systemic broad-spectrum penicillin (or azithromycin) and a minimum look-back period of at least one year at the time of the first prescription. Only the first prescription date for either of the two types of antibiotics will be considered. Patients with a concomitant first prescription for both a systemic fluoroquinolone

and a systemic broad-spectrum penicillin (or azithromycin), and patients with a history of TTP will not be considered.

The patients will then be followed for a maximum of 30 days (a sensitivity analysis will follow patients up to 60 days) and any occurrence of TTP during this time period will be recorded. (The 60-day sensitivity analysis will be done to allow time for the recording of what is a secondary care diagnosis in the primary care databases.) Patients with a history of HIV, disseminated intravascular coagulation (DIC) or haemolytic-uremic syndrome (HUS) will be excluded as these conditions can lead to TTP. The follow-up of the patients will end at the earliest of:

- A TTP outcome event
- End of follow-up (30 or 60 days)
- Use of the alternative treatment (from a fluoroquinolone to a broad-spectrum penicillin and vice versa)
- Occurrence of HIV, DIC or HUS
- End of observation (patient no longer observable in the database)

4.2. Setting

The proposed settings are GP practices (in IMRD-UK) and GP and specialist practices (in IMS® Disease Analyzer Germany).

4.3. Variables

4.3.1. Exposure variables

4.3.1.1. Systemic fluoroquinolones

Systemic fluoroquinolones (oral, parenteral, inhalation) in WHO ATC class J01MA (Fluoroquinolones) will be included. In IMS® Disease Analyzer Germany medicines the relevant products can be identified using the EphMRA ATC code J01G (systemic fluoroquinolones). In IMRD-UK systemic fluoroquinolones can be identified by ATC class (J01M A) and by search generic drug names in the database.

The list of identified systemic fluoroquinolone products in IMS® Disease Analyzer Germany can be found in Annex 1. The list of identified systemic fluoroquinolone products in IMRD-UK can be found in Annex 2.

4.3.1.2. Systemic broad-spectrum penicillins

Systemic broad-spectrum penicillins in WHO ATC class J01CA and J01CR (Combinations of penicillins, including beta-lactamase inhibitors) will be included. In IMS® Disease Analyzer Germany medicines the relevant products can be identified using the EphMRA ATC code J01C (broad spectrum penicillins). In IMRD-UK systemic broad-spectrum penicillins can be identified using ATC code "J01C A" OR "J01C R".

The list of identified systemic broad-spectrum penicillins in IMS® Disease Analyzer Germany can be found in Annex 3. The list of identified systemic broad-spectrum penicillin products in IMRD-UK can be found in Annex 4.

4.3.1.3. Azithromycin

Systemic azithromycin with the WHO code J01FA10 will be included. In IMS® Disease Analyzer Germany medicines the relevant products can be identified using the EphMRA ATC code J01F (macrolides and similar types) and selecting the molecule 'azithromycin'. In IMRD-UK systemic broad-spectrum penicillins can be identified using ATC code "J01F A10".

4.3.2. Outcome variables

TTP will be identified using ICD 10 code M31.1 (Thrombotic microangiopathy) in IMS® Disease Analyzer Germany. In a sensitivity analysis, the ICD10 code D59.4 (Other nonautoimmune haemolytic anaemias) will be added to this.

In IMRD-UK TTP will be identified through the use of Read codes corresponding to ICD10 code M31.1:

- G756.00 "Thrombotic microangiopathy";
- G756000 "Moschowitz syndrome";
- G756100 "Thrombotic thrombocytopenic purpura";
- G756z00 "Thrombotic microangiopathy NOS"

In a sensitivity analysis, Read codes corresponding to ICD10 code D59.4 will also be included:

- D111.00 Non-autoimmune haemolytic anaemia
- D111000 Mechanical haemolytic anaemia
- D111100 "Microangiopathic haemolytic anaemia";
- D111200 Toxic haemolytic anaemia
- D111y00 Other specified non-autoimmune haemolytic anaemia
- D111z00 Non-autoimmune haemolytic anaemia NOS

4.3.3. Variables for exclusion of patients

4.3.3.1. HIV

In IMS® Disease Analyzer Germany HIV will be identified using ICD 10 codes B20-B24. In IMRD-UK HIV will be identified using codes Read codes starting "A788...", "A789..." or by Read codes "43C3.11", "Eu02400" or "L179.00".

4.3.3.2. Disseminated intravascular coagulation (DIC)

In IMS® Disease Analyzer Germany DIC will be identified using the ICD 10 code D65. In IMRD-UK DIC will be identified using Read code D306.12 "Disseminated intravascular coagulation".

4.3.3.3. Haemolytic-uremic syndrome (HUS)

In IMS® Disease Analyzer Germany DIC will be identified using the ICD 10 code D59.3. In IMRD-UK HUS will be identified using Read code D111300 "Haemolytic-uraemic syndrome"

4.4. Data sources

4.4.1. IMS® Disease Analyzer Germany

IMS® Disease Analyzer Germany (IMS Germany) version December 2020 will be used for the analysis. IMS Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of GP practices are included in IMS Germany from the different regions in Germany. Data from IMS Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases [1, 2]. This study will include all practices prescribing the antibiotics of interest and will not be restricted to GP practices only.

Diagnoses are coded using WHO ICD 10 codes, and prescriptions are coded using EphMRA ATC codes and substance names.

4.4.2. IMRD-UK

IMRD-UK contains longitudinal electronic patient records extracted from the VISION practice management software, which has been contributed to by > 790 general practices across the United Kingdom covering up to 6% of the UK population. Data are largely representative of the UK population in terms of age, sex, deprivation status, and geographic distribution. It contains GP prescriptions with medicinal products identified through a bespoke system of drug codes linked to generic drug names (substance names) or a substitute thereof in a drug and device dictionary. Records are available from 1986 onwards.

GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

4.5. Study size

The study will not be limited in size. All patients that fulfil the criteria for inclusion will be studied.

4.6. Data management

All analyses will be carried out using SAS Enterprise Guide version 7.15.

4.7. Data analysis

The incidence rate of TTP will be calculated from the number of patients with TTP during the follow-up period and the total follow-up time in years of follow-up in each of the two treatment groups. The 95% confidence intervals for the incidence rates will also be calculated.

Incidence rate = number of patients with TTP ÷ person-time of follow-up in years

In addition, the treatment groups will be compared in terms of age and gender structure (percentage of males/females, percentage of patients by 10-year age groups, mean age, median age). If there are sufficient numbers of events, we will also compare the age and gender structure between patients with and patients without TTP.

For IMRD-UK the study period will be limited to the years 2000 onwards as the TTP diagnosis was seldom used before that date.

For both IMS® Disease Analyzer Germany and IMRD-UK, patients with a history of conditions known to be associated with TTP will be excluded. These will be HIV, Disseminated Intravascular Coagulation (DIC) and Haemolytic Uremic Syndrome (HUS).

It is likely that there will be low numbers of events in the relatively short time windows following exposure: if this occurs, consideration will be given to pooling data from the German and UK data sources to avoid displaying any low cell counts.

4.8. Quality control

The quality of IMS® Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis. IMRD-UK contain a number of flags indicating potential data issues in the patient, practice, prescribing and clinical (diagnosis) datasets. The analysis will be restricted to data that are “acceptable” and practices will only be included once they reach the Acceptable Mortality Reporting (AMR) date.

4.9. Limitations of the research methods

4.9.1. IMS® Disease Analyzer Germany

In Germany the patient has free physician choice: in IMS Germany patients can only be followed for as long as they continue to visit the same physician as patients are not identifiable across physician practices for confidentiality reasons. Furthermore, as the patient can visit several physicians concurrently, collected data may be incomplete. Moreover, the completeness of data on outcomes may depend on the extent to which outcomes are captured in primary care vs. secondary care and TTP is a diagnosis likely to be made in secondary care.

4.9.2. IMRD-UK

IMRD-UK holds primary-care electronic healthcare records. TTP is a diagnosis that will very likely be made – at least in part – in secondary care. As such, the completeness of recording of this diagnosis will be dependent on primary care records being updated to reflect secondary care diagnoses. Although this would be expected for what is a serious condition, we are not aware that the diagnosis of TTP has been validated in IMRD-UK or other primary care databases in the UK.

5. Protection of human subjects

IMS® Disease Analyzer Germany is a de-anonymized database with electronic health records. No ethics committee approval is required. For IMRD-UK a study protocol must be approved by the Scientific Review Committee (SRC) and the final report approved by IQVIA before the results can be put in the public domain. In doing this, consideration is given to both the scientific validity of the proposal and data privacy with low cell counts (1-5) being suppressed to prevent identification of individuals.

6. Plans for disseminating and communicating study results

Results of the study will be published in the EU-PAS register.

7. References

1. Moore, J., et al., *Moxifloxacin-Induced Thrombocytopenia Mediated by Moxifloxacin-Dependent IgM and IgG Antiplatelet Antibodies: A Case Report*. *Cureus*, 2020. **12**(9): p. e10507-e10507.
2. Cheah, C.Y., B. De Keulenaer, and M.F. Leahy, *Fluoroquinolone-induced immune thrombocytopenia: a report and review*. *Internal Medicine Journal*, 2009. **39**(9): p. 619-623.
3. Hashmi, H.R.T., et al., *Ciprofloxacin-Induced Thrombotic Thrombocytopenic Purpura: A Case of Successful Treatment and Review of the Literature*. *Case Reports in Critical Care*, 2015. **2015**: p. 143832.
4. Landi, A.J. and R. Burkes, *Probable Levofloxacin-Induced Thrombocytopenia in a Patient Previously on Ciprofloxacin: A Case Report and Literature Review*. *Case Reports in Medicine*, 2016. **2016**: p. 2860645.
5. Sim, D.W., et al., *Ciprofloxacin-induced immune-mediated thrombocytopenia: No cross-reactivity with gemifloxacin*. *Journal of clinical pharmacy and therapeutics*, 2018. **43**(1): p. 134-136.

8. Annexes

8.1. Annex 1

List of identified systemic fluoroquinolone products in IMS® Disease Analyzer Germany

Ciprofloxacin-containing products

Product name	Therapy Numbers
BAYCIP E-M>>	GE1349170, GE1394242, GE1494065, GE2358814
BAYCIP EUP>>	GE2553057
BAYCIP KHP>>	GE1232125, GE1305289, GE243820, GE516582
BAYCIP MTK>>	GE1493960, GE377107
CIPRO BASICS	GE10149155, GE13113973, GE13272512, GE1397833, GE14062949, GE14064442, GE1427567, GE1810267, GE1836966, GE192228, GE217177, GE320730, GE94607, GE9841809
CIPRO LICH	GE209513, GE44444, GE55604, GE81641, GE82574, GE82890
CIPRO-1A PHARMA	GE364197, GE3897909, GE3904382, GE391612, GE3940781, GE3960485, GE433460, GE574133, GE6534305, GE6596280, GE7339960
CIPRO-ACIS	GE2173370, GE252921, GE25700, GE416223
CIPROBAY	GE11024143, GE1204146, GE133409, GE1403939, GE1531805, GE274270, GE285192, GE340076, GE364482, GE376328, GE392844, GE43948, GE47932, GE581444, GE6030, GE6061, GE6069, GE6070, GE6071, GE6072, GE642668
CIPROBAY AC9>>	GE1770766, GE1887673, GE1954286, GE2478572, GE3479147, GE415080, GE533857, GE620100
CIPROBAY BRA>>	GE1414409, GE1571619, GE1812579, GE2302664, GE2511517, GE2722144, GE2862948, GE3144854, GE3180038, GE3261350
CIPROBAY E-M>>	GE11468800, GE11557777, GE1188692, GE1401276, GE1423189, GE1463074, GE157901, GE1593432, GE1872256, GE212235, GE2767053, GE281552, GE37099, GE65603, GE69182, GE73495
CIPROBAY EUP>>	GE1230321, GE154614, GE1608730, GE2761899, GE278959, GE3211662, GE3260867, GE459840, GE507778, GE564126, GE578543, GE690912, GE812870, GE82309

Product name	Therapy Numbers
CIPROBAY KHP>>	GE1042753, GE1420377, GE151782, GE151828, GE154682, GE283152, GE283380, GE365748, GE682041, GE7484202, GE82906, GE9282
CIPROBAY MTK>>	GE172226, GE360676, GE382168, GE396251, GE48303, GE90133
CIPROBAY MVT>>	GE1646247, GE1646375, GE1715553, GE1954463, GE2011150, GE2011364
CIPROBAY ORI>>	GE165705, GE184005, GE225830, GE2302945, GE3407124, GE3892213, GE4021200, GE423203, GE682315, GE957687
CIPROBETA	GE11200698, GE1554906, GE268717, GE47090, GE52778, GE61985, GE68309, GE88728, GE9756029, GE9806403, GE9986865, GE9994910
CIPRODOC AD2	GE9271474, GE9273893, GE9391238, GE9392205
CIPRODOC DOC	GE1301567, GE1532520, GE2324006, GE288008
CIPRODURA	GE111022, GE154128, GE156360, GE204689, GE219026, GE51221, GE54532, GE8991718, GE9179566
CIPROFAT	GE3121416, GE3649027, GE531254, GE534123
CIPROFAT (RER)	GE10301668, GE10310677, GE10316635, GE10335001
CIPROFL.CLARIS DM+	GE9634095
CIPROFL.CLARIS P0E	GE8857124
CIPROFL.CLARIS P6M	GE14615257, GE15291218
CIPROFLO.RAT.A8K>>	GE4646599, GE4715616, GE4734816, GE4798277
CIPROFLO.RAT.E-M>>	GE5575564, GE5617714, GE5629024, GE6009485
CIPROFLO.RAT.EUP>>	GE272005, GE375437, GE436146, GE682961
CIPROFLO.RAT.ORI>>	GE5539351, GE5546040, GE5629373, GE5931174
CIPROFLOX PUREN	GE154935, GE155310, GE198392, GE208064, GE340270
CIPROFLOX TAD	GE8064140
CIPROFLOX-CT	GE10095639, GE42387, GE46171, GE46655, GE55868, GE61252
CIPROFLOX.HEU WB-	GE4197767
CIPROFLOX.HEUM.H2U	GE9217272, GE9228803, GE9268165, GE9323759
CIPROFLOX.HEUM.HEU	GE10020419, GE10116898, GE10359994, GE13685279, GE13687460, GE13767840, GE14145225, GE154409, GE193502, GE206283, GE57211, GE88172, GE9793627
CIPROFLOX.HEUM.NO&	GE10599120, GE9518016, GE9518723, GE9564220, GE9715670, GE9783595, GE9807149
CIPROFLOXA.ATV(DM+	GE10720217, GE11635277, GE7263567, GE7279210, GE7299703, GE7353774
CIPROFLOXA.DM+ ALT	GE7051350, GE7093797, GE7095294, GE7201432
CIPROFLOXA.FAIR-M	GE13649559, GE13813281, GE14005890, GE14121247, GE14168811, GE14169575, GE14239092, GE14537980, GE14822593
CIPROFLOXA.FARMAPL	GE18832937, GE18907765
CIPROFLOXAC.ACCEDO	GE5503693, GE5598045, GE5627928, GE5802370
CIPROFLOXAC.AXSAN	GE3355981
CIPROFLOXAC.HEC PH	GE15173731, GE15237529, GE15325217, GE15494390, GE15544100, GE15859033, GE15865802, GE16137850, GE16258233, GE16278007, GE16605458, GE16859423, GE16998496
CIPROFLOXAC.HIKMA	GE7333344
CIPROFLOXAC.R(DOL)	GE16211641, GE16253221, GE16540168, GE16940720, GE18519687
CIPROFLOXAC.RE.ALT	GE1471277, GE1953970, GE2013904, GE205423, GE215546, GE2491950, GE274405, GE3474687, GE491082, GE557863, GE7423961, GE7798762
CIPROFLOXAC.SANDOZ	GE10411, GE111907, GE1571448, GE212045, GE25530, GE2705674, GE85257
CIPROFLOXACI.ALMUS	GE7001064, GE7193894, GE7212995, GE7289106

Product name	Therapy Numbers
CIPROFLOXACI.STADA	GE166131, GE196623, GE19802, GE25791, GE39228, GE4523, GE5002
CIPROFLOXACIN AZU	GE148439, GE156138, GE157574, GE196699, GE420105, GE88437, GE88996
CIPROFLOXACIN BAX	GE6914321, GE7802610
CIPROFLOXACIN DO3	GE15753612, GE15957233
CIPROFLOXACIN EBH	GE6265649, GE6415659, GE6603435, GE7432698
CIPROFLOXACIN KSK	GE1000999, GE153167, GE209994, GE4495784, GE4535470, GE4678637, GE729815
CIPROFLOXACIN SOH	GE1463949, GE29505, GE3500138, GE364154, GE37078, GE442454, GE63004
CIPROFLOXACIN ABZ	GE1201399, GE508609, GE5295586, GE5870804, GE790495, GE852267
CIPROFLOXACIN AL	GE16439928, GE16468625, GE16525851, GE16637598, GE16649513, GE176882, GE1812764, GE1865273, GE200958, GE26755, GE278680, GE302029
CIPROFLOXACIN ARIS	GE5217268, GE8744236, GE8808568, GE8812771, GE8844263, GE8854385, GE8991668, GE9047673, GE9178752, GE9217441
CIPROFLOXACIN AURU	GE10045612, GE8325464, GE8407836, GE8595655, GE8609709, GE9034186, GE9173942, GE9180497, GE9237325, GE9243674, GE9934092
CIPROFLOXACIN AWD	GE2793446, GE327866, GE3610, GE445039
CIPROFLOXACIN AXC.	GE10012776, GE10229410, GE4240678, GE4276050, GE4288432, GE4352048, GE9874932, GE9937759
CIPROFLOXACIN KABI	GE11430859, GE5704929, GE6988192, GE8658027, GE9480638
CIPROFLOXACIN NORM	GE16275170, GE16941188
CIPROFLOXACIN TAD	GE153855, GE160090, GE174588, GE195678, GE195690
CIPROFLOXACIN TEVA	GE12198510, GE14390642
CIPROFLOXACIN-BIOM	GE6683619, GE6687578, GE6734611, GE6760805, GE6806297, GE6902179, GE7291124
CIPROFLOXACIN-CHEP	GE8098976, GE8120145
CIPROFLOXACIN-RAT.	GE13965, GE15604018, GE340044, GE38474, GE423523, GE45762, GE49359, GE56930, GE9924530
CIPROFLOXACIN-UROP	GE2786718, GE2786720, GE921649, GE965870
CIPROGAMMA	GE326548, GE369292, GE419267, GE42389, GE569431
CIPROHEXAL	GE10107619, GE154206, GE222415, GE34479, GE3771925, GE3778815, GE3780092, GE3791537, GE5579569, GE5869478, GE5887828, GE61808, GE75556, GE85346, GE86914, GE9914949
CIPROVERT	GE11552419
CIPROX	GE2330954, GE2722825, GE2956902, GE377069
CIPROXIN KHP>>	GE843554, GE970419, GE970479
GYRACIP	GE1043020, GE1387745, GE1832656, GE305476, GE3861205, GE691011, GE7315258, GE7326830, GE7431850, GE7576234, GE7908148
GYRASTOP	GE1700909, GE198506, GE198523, GE244725, GE333684, GE505295
INFECTOCIPRO	GE4808601, GE4818886, GE4832726, GE4985514, GE6772769, GE7258635, GE7279430, GE7528677
KECIFLOX	GE1191625, GE1202421, GE213686, GE27306, GE365795, GE51983, GE91036
UTIMINX	GE9432753

Levofloxacin-containing products

Product name	Therapy Numbers
LEVITIS	GE14800131, GE18406075

Product name	Therapy Numbers
LEVOFLOX-CT	GE10718816, GE10719797, GE10725450, GE10725677, GE10725905, GE10734301, GE10740790
LEVOFLOX-DENK	GE17186234
LEVOFLOX-HEC	GE17780211, GE17847224, GE17872806, GE17940543, GE18033296, GE18149890
LEVOFLOXA.MACL.MA5	GE19163237
LEVOFLOXAC.HEC PH.	GE15130904, GE15151009, GE15250781, GE15450562, GE15888675, GE15940333, GE19577376, GE19604955, GE19712535, GE19744621, GE19760811, GE19802049
LEVOFLOXACIN DO3	GE15429707
LEVOFLOXACIN ABZ	GE10720939, GE10744058, GE10752974
LEVOFLOXACIN AL	GE10541423, GE10549904, GE10568290, GE10643015, GE10708668, GE10740288, GE10745649
LEVOFLOXACIN AMNEA	GE18737469
LEVOFLOXACIN ARIST	GE11613163, GE11614494, GE11628998, GE11632390, GE11636771, GE11706466, GE12086094
LEVOFLOXACIN AUROB	GE12736580, GE12789790, GE12895938, GE13318876, GE13574811, GE13594643, GE13937001
LEVOFLOXACIN BLUEF	GE10964400, GE10970720, GE11039529, GE11344865, GE11469657, GE11808564, GE5385177
LEVOFLOXACIN DENK	GE11049285, GE11176193, GE14392235, GE14494281
LEVOFLOXACIN DURA	GE10725837, GE10740622, GE10783859, GE10783860, GE10811531, GE10960672
LEVOFLOXACIN EBER.	GE10895041, GE16861117, GE17785433, GE18751336
LEVOFLOXACIN HEUM.	GE10546907, GE10573505, GE10593715, GE10594310, GE10647645, GE13822239, GE5385402
LEVOFLOXACIN HEXAL	GE10540968, GE10541479, GE10542604, GE10545173, GE10545709, GE10546135, GE10558218, GE10977016, GE12709557
LEVOFLOXACIN HOSPI	GE15374365
LEVOFLOXACIN IBISQ	GE16328413, GE19643320
LEVOFLOXACIN KABI	GE10931563, GE13805740
LEVOFLOXACIN RATIO	GE10544630, GE10546872, GE10556233, GE10563154, GE10575993, GE11255998, GE5227610
LEVOFLOXACIN STADA	GE10552809, GE10554028, GE10562553, GE10563734, GE10567359, GE10585263, GE5328015
LEVOFLOXACIN-1A PH	GE10540761, GE10578083, GE10581859, GE10607712, GE10630439, GE11069242, GE1943847, GE5417627, GE5419182
LEVOFLOXACIN-ACTAV	GE10558593, GE10769207, GE10783208, GE10836152, GE10875260, GE11054260, GE11181161, GE11710356, GE14646899
LEVOFLOXACIN-HAMEL	GE16149942
QUINSAIR ALT	GE16138296
QUINSAIR (HZP)	GE16862996
QUINSAIR KHP>>	GE19544060
TAVANIC	GE1305645, GE1344642, GE164078, GE2202065, GE2250323, GE272013, GE28770, GE29645, GE29723, GE53755, GE6969, GE71420, GE911
TAVANIC E-M>>	GE2437943
TAVANIC MZG>>	GE2094563

Moxifloxacin-containing products

Product name	Therapy Numbers
ACTIMAX	GE1504895, GE34571, GE49330, GE524016
ACTIRA E-M>>	GE9042453, GE9364145, GE9466882
ACTIRA EUP>>	GE10244393, GE7808347
ACTIRA KHP>>	GE8717259, GE8981167
AVALOX	GE109528, GE1528285, GE185001, GE3062, GE4529686
AVALOX A4X>>	GE6791138, GE6795921, GE8640809
AVALOX AC9>>	GE8769227, GE8817258
AVALOX BRA>>	GE4488895, GE4585926, GE4625312
AVALOX CC4>>	GE10469976, GE10583714, GE12676670, GE16635844, GE16646303, GE16723293
AVALOX E-M>>	GE6024978, GE6091224, GE6281637
AVALOX EUP>>	GE3727491, GE3788080, GE3882617
AVALOX GRK>>	GE13208246, GE13253669, GE13254619
AVALOX KHP>>	GE1387750, GE261822, GE4098087
AVALOX ML8>>	GE10047820, GE10051703, GE10083955
AVALOX MVT>>	GE6696290, GE6731581, GE6767937
AVALOX ORI>>	GE3710516, GE3714400, GE3762985
AVELOX A4X>>	GE7870026, GE7904917
AVELOX AC9>>	GE10202987, GE9930096, GE9999569
AVELOX CC4>>	GE10429954, GE10805408, GE10903707
AVELOX E-M>>	GE3675705, GE3680147, GE7663979
AVELOX EUP>>	GE8814372, GE8865263, GE9696687
AVELOX GRK>>	GE13183298, GE13602170, GE13697583
AVELOX KHP>>	GE3675688, GE3904705, GE4071115
AVELOX ORI>>	GE4455909, GE4563642, GE5688675
MOXIFLOX.NORID.DO3	GE15998726
MOXIFLOX.STADA AM6	GE14329018
MOXIFLOX.STADA SAD	GE14282575, GE14490320, GE14560569, GE16213160
MOXIFLOXAC.HEC PH.	GE16244725, GE16250102, GE16264627, GE16267050, GE16342380, GE16541309
MOXIFLOXACIN ABZ	GE14367206, GE14375216, GE14389505, GE14469092
MOXIFLOXACIN AL	GE14283431, GE14344915, GE14487803
MOXIFLOXACIN ARIST	GE10284755, GE18904969, GE18913095, GE18950336
MOXIFLOXACIN AUROB	GE14159394, GE14269577, GE15459991
MOXIFLOXACIN HEUM.	GE14456054, GE14456288, GE14532119, GE19693780, GE19773954
MOXIFLOXACIN HEXAL	GE14362023, GE14371378, GE14528708, GE14921291
MOXIFLOXACIN HOLST	GE16753373, GE16877292, GE16976922, GE19878886
MOXIFLOXACIN IBISQ	GE15234094
MOXIFLOXACIN INRES	GE16143672, GE18325357
MOXIFLOXACIN KABI	GE16439751
MOXIFLOXACIN M.LAB	GE17389120
MOXIFLOXACIN PUREN	GE16508214, GE16543376, GE16737169, GE19528199
MOXIFLOXACIN TAD	GE14277758, GE14292947, GE14312910
MOXIFLOXACIN TILL.	GE18827333, GE18896187, GE19798192, GE19884778
MOXIFLOXACIN-1A PH	GE14288018, GE14296985, GE14302319, GE16811211
MOXIFLOXACIN-ACTAV	GE14254441, GE14272829, GE14278080

Product name	Therapy Numbers
MOXIFLOXACIN-RATIO	GE14287213, GE14298590, GE14428369, GE14503997

Ofloxacin-containing products

Product name	Therapy Numbers
GYROFLOX	GE215375, GE2357008, GE2422041, GE257033, GE2821792, GE2956447
OFLO TAD	GE1631108, GE1894928, GE7978082
OFLODURA	GE155309, GE155843, GE183734, GE264535, GE379326, GE51214
OFLOHEXAL	GE157056, GE1592667, GE159511, GE160692, GE450840
OFLOX AZU	GE149410, GE338357, GE89696
OFLOX BASICS	GE338767, GE373951, GE420185, GE450867, GE47847, GE88950, GE9725745
OFLOX CT	GE422344, GE46061, GE46250, GE56868, GE83727
OFLOX PUREN	GE1704593, GE1954632, GE2160507
OFLOX SANDOZ	GE116671, GE302287, GE434672, GE653590
OFLOX-WOLFF	GE1955400, GE1993936, GE2011484
OFLOXACIN SOH	GE100760, GE113308, GE1880252, GE2814215, GE430233, GE64595
OFLOXACIN ABZ	GE128656, GE1508955, GE1582655, GE1604389
OFLOXACIN AL	GE106225, GE1405562, GE154084, GE155842, GE1776916
OFLOXACIN BILLIX	GE8769762, GE8850437, GE9907700
OFLOXACIN HEUMANN	GE2440630, GE326225, GE3867429, GE450285, GE670217, GE8694187, GE8710793, GE8752136
OFLOXACIN HOECHST	GE1647920, GE375640
OFLOXACIN STADA	GE153383, GE338687, GE338704, GE46211, GE48110, GE65708
OFLOXACIN-1A PHARM	GE4430778, GE4459752, GE4484948, GE4488411, GE4524467
OFLOXACIN-RA.E-M>>	GE5542379, GE5659204, GE5734471, GE6599201
OFLOXACIN-RA.EUP>>	GE4439258, GE4467045, GE4522220, GE4539829, GE4995365, GE6336044
OFLOXACIN-RATIOPH.	GE152796, GE16308, GE22371, GE301431, GE30263, GE46382, GE498104, GE56837
OFLOXACINE-R.E-M>>	GE5560589, GE5898113
OFLOXBETA	GE264489, GE372990, GE400932
SURNOX KHP>>	GE1538794, GE1647440, GE1646777
TARIVID	GE1061624, GE1181020, GE1420948, GE144076, GE205278, GE28607, GE28608, GE28609, GE34103, GE715455
TARIVID A+S>>	GE360779, GE528294
TARIVID A1H>>	GE1040197, GE1040565, GE1050169
TARIVID AC9>>	GE1195056, GE350078, GE72209
TARIVID ARW>>	GE743007, GE892008
TARIVID BRA>>	GE536912, GE536913, GE848334
TARIVID CM/>>	GE1772467, GE2439873
TARIVID E-M>>	GE1516637, GE155432, GE160342, GE503624, GE573230, GE982006
TARIVID EUP>>	GE1296603, GE1329540, GE284589, GE536797, GE536910, GE568475
TARIVID GPP>>	GE1215181, GE379327, GE429601
TARIVID GRK>>	GE391869, GE893123
TARIVID GWL>>	GE434936, GE456564, GE536819
TARIVID KHP>>	GE113961, GE116677, GE156285, GE340200, GE71032
TARIVID ME->>	GE1439368, GE266719

Product name	Therapy Numbers
TARIVID MTK>>	GE172384, GE63743, GE707764
TARIVID MVT>>	GE1023179, GE703510
TARIVID ORI>>	GE229211, GE847236
TARIVID OTI>>	GE1166312, GE468863, GE980984
TARIVID PW9>>	GE1099510
TARIVID REA>>	GE1016448
TARIVID SVP>>	GE1297359, GE536798
URO TARIVID	GE107959

Norfloxacin-containing products

Product name	Therapy Numbers
BACTRACID	GE29315, GE432600, GE4962
BARAZAN (MSD)	GE4620599, GE4779163, GE4822247
BARAZAN (DKM)ALT	GE120352, GE80846, GE80847
BARAZAN (MSD)ALT	GE3555, GE3556, GE3557
FIRIN	GE11375, GE19367, GE254566, GE395965
NORFLOHEXAL	GE379604, GE46132, GE53652, GE8695
NORFLOSAL	GE191750, GE3178, GE432658, GE93466
NORFLOX AZU	GE254516, GE260168, GE340175, GE395583
NORFLOX URM	GE209900, GE422876, GE45482
NORFLOX CT	GE1384813, GE170280, GE187390
NORFLOX PUREN	GE106009, GE208105, GE508836
NORFLOX SANDOZ	GE1365424, GE3369537, GE365992, GE91863
NORFLOX-1A PHARMA	GE11140220, GE152664, GE37342, GE421741
NORFLOXA.RAT.E-M>>	GE6070057, GE6230202, GE6279890
NORFLOXA.RAT.EUP>>	GE4436476, GE4496043, GE4530694
NORFLOXACIN ACS	GE1192038, GE368422
NORFLOXACIN SOH	GE357327, GE47697, GE832638
NORFLOXACIN ABZ	GE10092783, GE269514, GE89309
NORFLOXACIN AL	GE16648914, GE207287, GE278163, GE334067
NORFLOXACIN HEUM.	GE507959, GE508864, GE516178
NORFLOXACIN STADA	GE1208482, GE232262, GE254446, GE415708
NORFLOXACIN-1A PH.	GE16393270, GE16449601, GE16473964
NORFLOXACIN-RATIO.	GE12744, GE443430, GE89797
NORFLOXBETA	GE153384
NORFLUXX	GE263716, GE362872, GE740076

Remaining fluoroquinolone products

Molecule	Product name	Therapy Numbers
Enoxacin	ENOXOR	GE27723, GE27834
Enoxacin	GYRAMID	GE13861, GE13864, GE13865, GE13866
Fleroxacin	QUINODIS	GE414986, GE503587, GE506987, GE800581
Gatifloxacin	BONOQ	GE170878, GE195647, GE195650, GE210032

Molecule	Product name	Therapy Numbers
Grepafloxacin	VAXAR	GE1053611, GE1053615, GE1053616, GE1065395
Pefloxacin	PEFLACIN	GE276695
Sparfloxacin	ZAGAM	GE1185833
Temafloxacin	TEFLOX	GE250582, GE250586, GE250587, GE250590, GE259469
Trovafloxacin	TROVAN	GE1166055, GE1166159

8.2. Annex 2

List of identified systemic fluoroquinolone products in IMRD-UK – To be completed shortly

8.3. Annex 3

List of identified systemic broad-spectrum penicillin products in IMS® Disease Analyzer Germany

Broad-spectrum penicillin-containing products

Products containing single substance amoxicillin

Product name	Therapy Numbers
ALOXYN (LTP)	GE1182, GE1183, GE1184
AMAGESAN (PBA)	GE196004, GE238264, GE376498, GE427964, GE862108
AMAGESAN (AES)ALT	GE1047522, GE1048957, GE1053925, GE1054118, GE1055162, GE1058205, GE1079199, GE828077
AMAGESAN (JOA)ALT	GE309560, GE316002, GE56968, GE724920, GE73155, GE73156, GE733139, GE733503, GE736442, GE737401, GE743245, GE747057, GE80047, GE80124, GE806365
AMC PUREN	GE1071342, GE1083127, GE186637, GE338104, GE391151, GE491632
AMOXI KS/	GE275708, GE341415, GE92319
AMOXI ABZ	GE317085, GE408384, GE410157, GE410175
AMOXI BASF	GE1477, GE1487, GE1495679, GE1500, GE1501, GE1502, GE33524, GE57069
AMOXI CT	GE13234, GE1480, GE1481, GE1482, GE1483, GE1484, GE1485, GE180802, GE246459, GE396109, GE465536, GE466, GE8000, GE817007
AMOXI HEFA	GE162343, GE169032, GE30803, GE486412, GE64767, GE80333, GE80428, GE87115, GE88967
AMOXI HEFA ALT	GE567891, GE631203, GE631204, GE670673, GE680772, GE813098
AMOXI HP	GE356849, GE785534, GE786462
AMOXI LICHTENSTEIN	GE1038133, GE1039865, GE1043188, GE1050285, GE855755, GE997629
AMOXI LUT	GE251527, GE289399
AMOXI PUREN HP	GE405777
AMOXI SANORANIA	GE631198, GE709924
AMOXI WOLFF	GE1491, GE1494, GE1495, GE1496, GE1497, GE1498, GE1499, GE299167, GE340292, GE44269, GE516471, GE67164
AMOXI-1A PHARMA	GE1573974, GE158586, GE162076, GE410100, GE564277, GE57955, GE71740, GE827149, GE8741714, GE8832454, GE8845722
AMOXI-DIOL(ENG)ALT	GE1172717, GE1200147, GE1202060, GE1212202, GE134195, GE186745, GE241834, GE538995

Product name	Therapy Numbers
AMOXI-DIOLAN ALT	GE1083211, GE309651, GE33537, GE33538, GE57079, GE57081, GE57082, GE57086
AMOXI-DIOLAN (BR&)	GE1201851, GE1221015, GE168799, GE199826, GE2286270, GE29047, GE413300, GE448257
AMOXI-INFANT	GE446597
AMOXI-LICH	GE403602, GE502362, GE68964, GE85587
AMOXI-SAAR	GE7800774, GE7813808, GE7847512, GE7876936, GE7894752, GE8074404
AMOXI-SANDOZ	GE1041208, GE138442, GE201880, GE235469, GE2723911, GE326573, GE498993, GE571421, GE988518
AMOXI-TABLINEN	GE1054707, GE226288, GE283752, GE30470, GE340805, GE409977, GE410171, GE57055, GE6380656, GE91811
AMOXIBETA	GE152926, GE183815, GE189881, GE190013, GE2072, GE277294, GE28851, GE306346, GE40631, GE420031, GE503046, GE68501, GE80050, GE81648, GE973806, GE992954
AMOXIBIOCI(DOR)ALT	GE134172, GE196855, GE269786, GE273633, GE295800, GE309634, GE316041, GE322391
AMOXIBIOGIN ALT	GE710347
AMOXIBIOGIN (G&H)	GE1062293, GE1066748, GE1066944, GE1091023, GE175383, GE527551, GE795760
AMOXICIL.RAT.E-M>>	GE4716583, GE4724564, GE4730906, GE4742801, GE4754299
AMOXICIL.RAT.EUP>>	GE13538, GE295229, GE65112, GE999165
AMOXICILL. RKR ALT	GE13193390
AMOXICILL.3MM(RKR)	GE134178, GE134180, GE134181, GE141434
AMOXICILL.HEUM.H2U	GE9125387, GE9133337, GE9220722, GE9241068, GE9253966, GE9322203, GE9358534, GE9413034, GE9532972
AMOXICILL.HEUM.HEU	GE100651, GE13669074, GE13928330, GE159872, GE161198, GE187138, GE196795, GE222365, GE284252, GE284555, GE289405, GE295809, GE316050, GE375522, GE404605, GE489450, GE82464, GE8714870, GE91041, GE9651929
AMOXICILLIN ACS	GE1298883, GE13619, GE144037, GE145223, GE2428, GE250217, GE265595, GE33597, GE413353, GE455345, GE88577
AMOXICILLIN AZU	GE36656
AMOXICILLIN HEY	GE275244, GE578331, GE641422, GE641423, GE670680
AMOXICILLIN IM3	GE1384296
AMOXICILLIN 1 SOH	GE1040664, GE165321, GE1989866, GE2344077, GE292949, GE3470300, GE4154820, GE4220413, GE436166, GE4425265, GE511045, GE631214, GE64646, GE66852, GE73228, GE80932, GE81313, GE9904482
AMOXICILLIN 2 SOH	GE103217, GE114279, GE1209256, GE13298085, GE1427301, GE14837204, GE1505, GE1633099, GE165314, GE1677010, GE1721809, GE1730094, GE1759632, GE191214, GE219111, GE2498628, GE2498668, GE2575104, GE2741964, GE293358, GE301963, GE308358, GE309641, GE3433617, GE3814718, GE399157, GE4169307, GE4511115, GE4585449, GE499993, GE50823, GE57072, GE5774975, GE619098, GE6297005, GE65873, GE691725, GE710869, GE7469841, GE85270
AMOXICILLIN ABZ	GE4374410, GE4417038, GE4533454, GE4539120
AMOXICILLIN AL	GE11534981, GE11560444, GE11614444, GE16547010, GE17239190, GE280795, GE327874, GE335109, GE335438, GE344235, GE344236, GE3989688, GE42043, GE87944, GE9251

Product name	Therapy Numbers
AMOXICILLIN ARISTO	GE15587892, GE15596709, GE15598266, GE15608080, GE15612608, GE15642047, GE15675650, GE15700821, GE15735675
AMOXICILLIN AXCOU.	GE7729835, GE8271000, GE9043310, GE9133639
AMOXICILLIN BASICS	GE1081727, GE147719, GE462756
AMOXICILLIN BILLIX	GE8687921, GE8703212, GE8787971, GE8823999, GE8831931, GE8864761, GE8914497, GE9399567
AMOXICILLIN DENK	GE16165607, GE16195305
AMOXICILLIN DURA	GE8055983, GE8149073, GE8646997, GE8663252, GE8674350, GE8764818
AMOXICILLIN MICR.L	GE15776759, GE15790779, GE15888612, GE16404810, GE16511286, GE16709044, GE16832012, GE16832475, GE17018009, GE17040528, GE17105555, GE17455154, GE17498168, GE17668467, GE18613548
AMOXICILLIN PB ALT	GE936484, GE940726, GE968786, GE970452, GE974990, GE980629
AMOXICILLIN PB(PBA	GE160665, GE178088, GE179111, GE339818
AMOXICILLIN STADA	GE1009, GE10405, GE11263, GE127017, GE1506, GE1507, GE1508, GE17819, GE240719, GE35170, GE50451, GE56230
AMOXICILLIN-RATIO.	GE127019, GE1503, GE1504, GE1510, GE1512, GE1513, GE1514, GE1517, GE182300, GE238987, GE297081, GE359788, GE405731, GE45230, GE46376, GE86848, GE90299
AMOXIDOC	GE1072644, GE579168
AMOXIHEXAL	GE124141, GE125130, GE134188, GE141795, GE1478, GE1520, GE1521, GE1522, GE1523, GE1524, GE192451, GE196858, GE327882, GE33533, GE378342, GE39933, GE417810, GE417879, GE4388786, GE4408785, GE46380, GE503660, GE57074, GE6680646, GE90291
AMOXIHEXAL EUP>>	GE6175900, GE6215686
AMOXILLAT	GE1212510, GE1525, GE1528, GE1529, GE1530, GE180852, GE33535, GE404288, GE503581, GE567161, GE73227
AMOXIMERCK MD3	GE1009739, GE1013416, GE1212203, GE1358480, GE358325, GE487863, GE598150, GE67260
AMOXIWIEB	GE161439, GE297284
AMOXYPEN	GE1322167, GE1531, GE1535, GE1537, GE1538, GE1539, GE1540, GE1541, GE1545, GE1549, GE1550, GE1551, GE1552, GE190413, GE231482, GE244532, GE251530, GE251531, GE5523, GE699610
BAKTOCILLIN	GE8092561
BYK AMOXICILLIN	GE174366
CLAMOXYL ALT	GE3934015
CLAMOXYL (B/W)	GE135181, GE135182, GE252120, GE35417, GE35418, GE506609, GE6140, GE6141, GE6142, GE6145, GE6146, GE6147, GE6148, GE652269
CLAMOXYL EUP>>	GE247156, GE35415
CUXACILLIN	GE7276, GE7278, GE7279
DIGNOAMOXICILLIN	GE653069, GE653070, GE663275, GE697987, GE708680, GE900434
DURA AX	GE11047, GE128841, GE36820, GE9697, GE9698, GE9699, GE9700, GE9701
EASYMOX	GE5780156, GE6187183
ESPA MOXIN	GE1085351, GE339250, GE527428
FLUI AMOXICILLIN	GE123966, GE158941, GE386854, GE393999
GLASSATAN	GE116544

Product name	Therapy Numbers
INFECTOMOX	GE111080, GE111081, GE157907, GE205455, GE217351, GE243110, GE25345, GE3581190, GE387211, GE4125077, GE7933, GE8594686, GE8656456, GE8971840, GE9174923
JEPHOXIN	GE623271, GE645497, GE655282, GE805586, GE870695, GE952238, GE958280
JUTAMOX	GE199401, GE338407, GE342211, GE342212, GE343932, GE343933, GE427644
OSPAMOX	GE247240, GE338981, GE338982, GE392018
PHAMOXI	GE1216447, GE338912, GE578429
SIGAMOPEN ALT	GE101798, GE26892, GE54716, GE78406, GE78407, GE88047, GE95525
SIGAMOPEN (PFZ)	GE2151695
SILAMOX (KPH)	GE189539, GE71573
ULCOLIND AMOXI	GE1023082, GE702262, GE715739

Products containing amoxicillin in combination with clavulanic acid

Product name	Therapy Numbers
ABICLAV LINDOPHARM	GE7040267, GE7061093
ABICLAV SOLUTAB	GE1656280, GE310079, GE3119153, GE3440234, GE3694176, GE999312
AMOCLAN EUP>>	GE3947956, GE4078182
AMOCLANHEXAL EUP>>	GE5906756, GE5924427
AMOCLAV	GE10152071, GE111654, GE11541, GE16209798, GE231195, GE25525, GE296928, GE3000, GE3614757, GE45271, GE4834007, GE533714, GE5651432, GE61184, GE700045, GE74064, GE9467
AMOX.CLAVULANS.A3P	GE7732613
AMOXCLAV HEXAL	GE10558174, GE10740579, GE11710141, GE17712652, GE7333627, GE7804387, GE8621200, GE9845632
AMOXCLAV-SAN.BBF>>	GE16613224, GE16656543
AMOXCLAV-SAN.ORI>>	GE6881120, GE7030721, GE7199245
AMOXCLAV-SANDOZ	GE1533902, GE1796989, GE1985391, GE2728387, GE2855883, GE289964, GE3875891, GE4160921, GE4212788, GE88745, GE88760
AMOXI-CLAV.HEUMANN	GE15541754, GE15560386, GE15599870, GE15647631, GE15670526
AMOXI-CLAV.STA.ALI	GE15259196, GE15498503
AMOXI-CLAV.STA.SAD	GE10101323, GE116273, GE12236, GE144977, GE150731, GE410772, GE414414, GE68447
AMOXI-CLAV.ZENTIVA	GE19950796, GE20051352, GE5398555
AMOXI-CLAVULAN AL	GE1397623, GE14906121, GE15027892, GE15131016, GE15197920, GE205460, GE320551, GE343564, GE683125, GE852045
AMOXI-CLAVULAN AUR	GE10883015, GE10900686, GE10911132, GE11802348, GE11846787
AMOXI-CLAVULAN PUR	GE19773877, GE19841869
AMOXI-SAAR PLUS	GE2431842, GE3229906, GE8938570, GE9185750
AMOXI.CLAVULAN.AAA	GE19808786, GE19808788
AMOXI.CLAVULAN.DEV	GE18315453, GE18335034, GE18361899
AMOXIC.CLAV.MICR.L	GE16880227, GE17160725, GE17505674, GE17546037, GE17811506, GE17950548
AMOXIC.PL.HEUM.NO&	GE12335135, GE14854394, GE9317523, GE9540339, GE9577584
AMOXIC.RAT.C.EUP>>	GE6758246, GE6784646, GE6788713, GE7276105, GE7300111
AMOXIC.RAT.C.ORI>>	GE7009631, GE7060532

Product name	Therapy Numbers
AMOXICI.PLUS EUP>>	GE6762064, GE6768938
AMOXICILL.COMP.ABZ	GE9818675, GE9853457, GE9859995, GE9900051
AMOXICILL.COMP.SOH	GE1169209, GE12815678, GE15721182, GE2299088, GE297158, GE3137331, GE3270630, GE3298860, GE3456702, GE3760427, GE4176291, GE4248303, GE4462589, GE4610631, GE690437, GE7713362, GE8192000
AMOXICILL.PLUS HEU	GE10237, GE2157617, GE3786482, GE3791212, GE8690139, GE8738106
AMOXICILL.RAT.COMP	GE10183, GE156868, GE162776, GE213075, GE298341, GE341701, GE55622
AMOXICLAV ACCEDO	GE3638550, GE3662412
AMOXICLAV ALKEM	GE17543811, GE17579932, GE17603372, GE17704773, GE17706868, GE17709143, GE17977622, GE18067149, GE18289787
AMOXICLAV ARISTO	GE14307643, GE14373222, GE15557628, GE15653962
AMOXICLAV AWD	GE4925378, GE4972035
AMOXICLAV BASICS	GE13748843, GE13792333, GE13913049, GE13930997, GE2066068, GE2137084
AMOXICLAV BETA	GE228399, GE259667
AMOXICLAV FAIR-MED	GE13634989, GE13680395
AMOXICLAV HIKMA	GE7866829, GE8478097
AMOXICLAV PUREN	GE1634822, GE236286, GE38383, GE46995
AMOXICLAV-1A PHARM	GE4157450, GE4171386, GE4242929, GE4372279, GE4871805, GE4962857, GE7642788, GE7734826
AMOXICLAV-CT	GE241198, GE31450, GE409772, GE4132791, GE414814, GE462147, GE690948
AMOXICLAV-ELPEN	GE19942865
AMOXICLAVULAN-1AP	GE3889461, GE3898582
AMOXIDURA PLUS	GE110793, GE14200, GE243404, GE367613, GE410765, GE47530, GE83613
AMOXILLAT CLAV	GE123907, GE157585, GE160414, GE168731, GE244678, GE2588691, GE404305, GE50368
AMOXIP.RAT.C.E-M>>	GE5538666, GE5591237, GE5601819, GE5649436, GE5655723
AMOXIP.RAT.C.EUP>>	GE1006026, GE158223, GE3153817, GE543517, GE978812
AUGMENTAN (B/W)	GE141719, GE166145, GE166146, GE170421, GE17308214, GE17363941, GE183556, GE2689788, GE3187, GE3188, GE3189, GE3190, GE3191, GE3192, GE410860, GE603712, GE61312, GE7170968, GE97383
AUGMENTAN A4X>>	GE16599480, GE16658948
AUGMENTAN AC9>>	GE7317297, GE7452346
AUGMENTAN EUP>>	GE1045882, GE169499
AUGMENTAN GRK>>	GE1990379
AUGMENTAN KHP>>	GE210982, GE338906, GE382649, GE425117, GE505645, GE507605, GE508967, GE574439, GE88593
AUGMENTAN MTK>>	GE1572114, GE1653156, GE1688570, GE210433, GE419606, GE421799, GE536404, GE854242
AUGMENTAN ORI>>	GE1573266, GE1716147, GE45698
AUGMENTIN AC9>>	GE2651736
AUGMENTIN BRA>>	GE2439127, GE2637514, GE522039, GE988325
AUGMENTIN E-M>>	GE1490910, GE1555793, GE1886953, GE2724556, GE2790824, GE2855632, GE2867930, GE3570505

Product name	Therapy Numbers
AUGMENTIN EUP>>	GE2790827
AUGMENTIN GRK>>	GE102972, GE1903196, GE244414, GE2886112
AUGMENTIN KHP>>	GE1088261
AUGMENTINE E-M>>	GE2695894, GE3865365, GE4985667
AUGMENTINE EUP>>	GE3483709, GE6115229
BIOCLAVID	GE1195073, GE213567, GE213591, GE328182, GE363195
CO-AMOXICLAV BLUEF	GE15307355, GE15328695, GE15387063, GE15478976
INFECTOSUPRAMOX	GE4426481, GE4427627

Products containing single substance ampicillin

Product name	Therapy Numbers
AMBLOSIN	GE342854
AMPENSAAR (GOM)	GE715899
AMPI ABZ	GE266638, GE849866
AMPI-TABLINEN 1000	GE65885
AMPICILLAT	GE1576, GE1577
AMPICILLIN B-C	GE631242
AMPICILLIN JNA	GE273646
AMPICILLIN SOH	GE16475547, GE2393562, GE3286316, GE39454, GE46400, GE6398381, GE73237, GE755726
AMPICILLIN WFF	GE165400, GE33550
AMPICILLIN ZVA	GE1580, GE46399, GE57098
AMPICILLIN HEXAL	GE114691, GE295827, GE46402
AMPICILLIN STADA	GE1147383, GE1581, GE33551, GE57097
AMPICILLIN-RATIOPH	GE143182, GE1582, GE1583, GE1584, GE1836907, GE210824, GE213015, GE2344935, GE344688, GE46397, GE572260, GE651024
BINOTAL ALT	GE103636, GE34722, GE4391, GE4392, GE4393, GE5520078, GE66539, GE66540, GE692133, GE73874
BINOTAL (BAY)	GE1060937, GE1215676, GE340042, GE425253
DURAAMPICILLIN	GE36831, GE36832
JENAMPIN	GE635388, GE635389
PEN-BRISTOL	GE983281
PENSTABIL M2P	GE1015501

Products containing ampicillin in combination with sulbactam

Product name	Therapy Numbers
AMPIC.SULB.ATV(DM+	GE13329216, GE7282014, GE7906641, GE8891600
AMPIC.SULB.DM+ ALT	GE3685382, GE4020499
AMPIC.SULBACT.AURO	GE15693628, GE15927498
AMPIC.SULBACT.EBER	GE16223989, GE16354567, GE16915743
AMPIC.SULBACT.IBIS	GE13555743, GE16877763, GE8346823
AMPIC.SULBACT.KABI	GE6556091, GE6941836, GE9596367
AMPIC.SULBACT.PURE	GE17531164, GE19024733
AMPIC.SULBACT.RAT.	GE7345484, GE8157373, GE8182538

Product name	Therapy Numbers
AMPIC.SULBACT.TEVA	GE10154506, GE9825673
AMPICILLIN HEX.COM	GE10832743, GE10904601, GE4276184, GE6527615, GE9260848
AMPICILLIN-RAT.COM	GE3754001, GE3915030, GE4070581
UNACID	GE1478146, GE174461, GE198348, GE2312470, GE423118, GE4932189, GE5004544, GE548640, GE835192

Products containing single substance piperacillin

Product name	Therapy Numbers
PIPERACILL.ATV(DM+	GE10769634, GE9247795
PIPERACILL.EBERTH	GE11437145, GE16551572, GE19639740, GE9086035
PIPERACILLIN FK2	GE1220539, GE3173572, GE4799068, GE9980840
PIPERACILLIN SOH	GE14960035
PIPERACILLIN HEXAL	GE1339356, GE1429105, GE2190740, GE362204
PIPERACILLIN HIKMA	GE15057370
PIPERACILLIN IBISQ	GE15879104, GE19171008
PIPERACILLIN-RATIO	GE2916984, GE3371925, GE5823832
PIPRIL	GE1254631, GE4021512

Products containing piperacillin in combination with tazobactam

Product name	Therapy Numbers
PIPERAC.COMP.HEXAL	GE11373870
PIPERAC.TAZOB.AURO	GE12913443
PIPERAC.TAZOB.EBER	GE13322932, GE16397840
PIPERAC.TAZOB.HEXA	GE13813027, GE17187377
PIPERAC.TAZOB.IBIS	GE16204730
PIPERAC.TAZOB.KABI	GE10710677, GE14537666
PIPERAC.TAZOB.NORI	GE16728236
PIPERAC.TAZOB.ORCH	GE9629641
PIPERAC.TAZOB.PFIZ	GE15021451
PIPERAC.TAZOB.PUR.	GE18597318
PIPERAC.TAZOB.RAT.	GE8313948
PIPERAC.TAZOB.STRA	GE10529400
PIPERAC.TAZOB.TEVA	GE15495560
TAZOBAC	GE1530924, GE2258536, GE2662546, GE4725205
TAZOCIN CC4>>	GE14115664

Products containing single substance sultamicillin

Product name	Therapy Numbers
SULTAMICILLIN-RAT.	GE11083962, GE11397813
UNACID PD	GE11049520, GE134543, GE180798, GE28994, GE81308, GE946821
UNASYN PD A4X>>	GE16856832, GE17210567
UNASYN PD AC9>>	GE19788473, GE19856915
UNASYN PD E-M>>	GE12492857, GE13107365

Product name	Therapy Numbers
UNASYN PD EUP>>	GE10313794, GE10542489
UNASYN PD KHP>>	GE15244674, GE15376650

Remaining products containing broad-spectrum penicillins

Molecule	Product name	Therapy Numbers
Amoxicillin + flucloxacillin	FLANAMOX	GE170317, GE87022
Ampicillin + oxacillin	LUCIPEN	GE4337420
Azlocillin	SECUROPEN	GE1006716, GE6392213, GE963110
Bacampicillin	AMBACAMP	GE1260, GE1261
Bacampicillin	PENGLOBE	GE101135, GE23573, GE53547, GE86971
Ciclacillin	ULTRACILLIN	GE8590125
Mezlocillin	BAYPEN	GE1212246, GE1238264, GE1307753, GE1351306, GE154994, GE157677, GE226513, GE289767, GE356147, GE681206, GE883832
Mezlocillin	MEZLOCILLIN CUN	GE857605
Mezlocillin	MEZLOCILLIN CARINO	GE16628332
Pivmecillinam + pivampicillin	MIRAXID	GE19644

8.4. Annex 4

List of identified systemic broad-spectrum penicillin products in IMRD-UK - To be completed shortly

9. Comments received on draft analysis plan

9.1. PRAC Member: Norway

In general we agree on the draft analysis plan. We support the study design.

We have no knowledge about the databases to be used in the study, the IMS Disease Analyzer Germany and the IMRD-UK. However, we notice the limitations described, and agree that

it is a limitation of the research method that the diagnosis of TTP is likely to be made in secondary care and may not be completely captured in primary care databases.

As regards outcome variables, only the ICD 10 code M31.1 (Thrombotic microangiopathy) is proposed to be used for the German database. We propose that the same diagnosis codes used for the UK database should also be applied to the German database:

The following codes are available in ICD-10 and should be included as outcome variables for the German database:

- *D59.4 Microangiopathic hemolytic anemia*
- *M31.1 Moschowitz' disease*
- *M31.1 Thrombotic thrombocytopenic purpura*

We suggest that patients with HIV should be excluded as HIV can lead to TTP. In addition, efforts should be taken to exclude cases of DIC and HUS as these syndromes can overlap with TTP.

EMA Response: Regarding microangiopathic hemolytic anaemia, we have now included a sensitivity analysis where also the ICD 10 code D59.4 (other nonautoimmune haemolytic anaemias) is included.

The proposed analysis could be considered as an analysis of narrow (codes that only include the condition of interest) and broad (including also overlapping codes that are not specific for the condition of interest) event definitions. Similarly, the analysis in IMRD-UK has been split into an analysis of narrow and broad TTP events.

We have also as you suggest excluded patients with HIV, DIC and HUS.

9.2. Country: Germany

We agree with the proposed Analysis plan and have some additional comments:

- *It is our understanding that the study refers only to incident users and that a patient is observed only once during the study period. The EMA is asked to briefly clarify if this is correctly understood or if the observation of multiple treatment periods is possible.*
- *If a patient is only observed once within the proposed study period, the EMA is asked to also provide information on incidence proportions.*
- *In some epidemiological studies focusing on FQs, azithromycin has often been used as a comparator. We wonder whether azythromycin could also be included in this data analysis, if feasible.*
- *In general we support the proposed study design. However, we would like to know, also in view of future analyses, whether the case-control design is generally suitable for the conduct of these rapid analyses. This is only because we would have expected a case-control design due to the rarity of the observed events.*

EMA Response: Regarding the first bullet point, it is correctly understood that a patient is observed only once during the study period.

Regarding the second bullet point, we could provide the proportion of cases with TTP as proportion of patients initiating treatment. Please let us know if this is not what you request, and you want instead

to know the number of patients who are excluded from the analysis because they are “prevalent” exposures.

Regarding the third bullet point, a comparison with azithromycin will also be provided.

Regarding the fourth bullet point, we don’t think the case-control approach has any advantage over the cohort design in most of the analyses we currently do. Our starting point is to assess the extent of drug exposure on the databases. From there we then assess whether the event of interest occurs in the exposed subjects. This is a logical order. As the potential harms of medicines are typically described as rates (for example in SmPCs as events per 100, 1000, 10000, etc.) an understanding of the extent of exposure is required and this naturally follows from having defined and then followed an exposed cohort. It should be noted that recent commentators have questioned the validity of the case control approach (see *Statistics in Medicine* 2019;38:4199–4208).