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COMMITTEE REPORT

Criteria for safety evaluation of antimicrobial agents

Japanese Society of Chemotherapy · Antimicrobial Agents Safety Evaluation Standards Committee · Akira Watanabe · Yutaka Tokue · Nobuki Aoki · Tetsuro Matsumoto · Katsunori Yanagihara · Futoshi Higa · Hiroyuki Tsuge · Masahito Nagashima · Hiromi Matsuoka · Yuji Sasagawa · Masato Matsumoto · Kazuo Fujimaki · Kenji Taguchi · Mari Ariyasu · Norifumi Yamamoto · Otohiko Kunii · Kohya Shiba

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Principles and basic concepts on the safety evaluation of antimicrobial agents

The Japanese Society of Chemotherapy criteria for assessment of adverse reactions and abnormal laboratory values associated with antibacterial agents in study subjects [1, 2] (hereinafter referred to as "JSC's current criteria"), have been adopted in many clinical studies from immediately after their publication and are also cited in areas other than antimicrobial agents. Accumulated safety data based on the criteria have been submitted to the regulatory authorities in Japan for marketing approval applications. No inquiries such as uncertainty about the safety evaluations in clinical studies of antimicrobial agents have been made so far; therefore, the criteria seem to be recognized widely, including by the regulatory authorities.

However, there is a concern that the JSC's current criteria do not fit the present situation, because in recent new drug development the results of overseas clinical studies

A. Watanabe
Research Division for Development of Anti-Infective Agents, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

Y. Tokue
Infection Control and Prevention Center, Gunma University Hospital, Maebashi, Japan

N. Aoki
Shinrakuen Hospital, Niigata, Japan

T. Matsumoto
Department of Urology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

K. Yanagihara
Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan

F. Higa
Department of Infectious, Respiratory, and Digestive Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan

H. Tsuge · H. Matsuoka
Daiichi-Sankyo Co., Ltd, Tokyo, Japan

M. Nagashima
Pfizer Japan Inc, Tokyo, Japan

Y. Sasagawa · M. Matsumoto
Meiji Seika Kaisha Ltd, Tokyo, Japan

K. Fujimaki · K. Taguchi
Toyama Chemical Co., Ltd, Tokyo, Japan

M. Ariyasu
Shionogi & Co., Ltd, Osaka, Japan

N. Yamamoto
Sanofi-Aventis K.K., Tokyo, Japan

O. Kunii
Teikyo University, Tokyo, Japan

K. Shiba
The Jikei University School of Medicine, Tokyo, Japan

A. Watanabe (✉)
Japanese Society of Chemotherapy, Nichinai Kaikan B1, 3-28-8 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
e-mail: karyo@jc4.so-net.ne.jp

have been used aggressively or global studies have been conducted.

The Antimicrobial Agents Safety Evaluation Standards Committee of the JSC (hereinafter, the "Committee") has developed a concept of "abnormal changes in laboratory values" while taking into account management of the results of studies by overseas pharmaceutical companies. This concept was developed for the purpose of maintaining consistency with Western safety evaluation from a global viewpoint. With regard to adverse events in terms of symptoms and findings, we have summarized the information on adverse events in clinical studies of antimicrobial agents approved for marketing after 2005 (see Tables 6, 7) and discussed evaluation points for adverse events that occurred frequently in clinical studies of antimicrobial agents.

Abnormal changes in laboratory values

Previously, when assessing whether or not changes in laboratory values were adverse events, we classified them into two groups: a shift from a normal to an abnormal value or an aggravation from the abnormal value before administration. From the perspective of maintaining consistency with the evaluation of overseas clinical study data and in order to be concise, however, we have established an assessment procedure that enables each laboratory test item to be evaluated by a Grade based on standard values for these items. Furthermore, in consideration that the JSC's current criteria have been adopted in many clinical studies and results have accumulated, we fully analyzed the available data from clinical studies and avoided causing a large discrepancy from current evaluation results. In particular, the assessment results when defining abnormal changes as Grade 2 or higher according to the "Common Terminology Criteria for Adverse Events v 3.0 JCOG/JSCO version" [3] (hereinafter referred to as the "CTCAE"), which are generally found to be similar to the JSC's current criteria, the abnormal changes tended to be consistent with the assessment results based on the JSC's current criteria. We decided that the classification specified in the CTCAE could be used to promote the optimum safety evaluation of antimicrobial agents.

Details of the establishment of criteria for abnormal changes in laboratory values have been published in the interim report of the Japanese Society of Chemotherapy, Antimicrobial Agents Safety Evaluation Standards Committee [4].

Symptoms/findings

Events related to "gastrointestinal disorders" are the most frequent adverse events in clinical studies of antimicrobial agents, followed by "respiratory, thoracic and mediastinal disorders," "skin and subcutaneous tissue disorders," "general disorders and administration site conditions," "infections and infestations," "musculoskeletal and connective tissue disorders," and "nervous system disorders" (see Table 6). In order to individually define the severity of each adverse event, as is done with the CTCAE, the Committee assumed that a comprehensive analysis based on clinical findings and epidemiological data for each specialized field would be necessary and that ensuring universality would be difficult. Therefore, in our report we decided to show comprehensive criteria for the assessment of severity, regardless of the individual symptoms and findings. This concept was also based on the idea that the opinions of the physicians who actually take charge of clinical studies would be appropriate for the assessment of the severity of adverse events and their causal relationships.

Criteria for safety evaluation of laboratory values

Method for evaluation of abnormal changes and adverse events

Criteria for abnormal changes in laboratory values are shown in Table 1. Based on these criteria, when laboratory values are within the range of abnormal changes, accompanying any adverse symptoms or findings, or possibly resulting in them, or requiring additional tests or treatment, they should be handled as adverse events, and the causal relationship with the investigational drug should be assessed.

Laboratory values are known to fluctuate in relation to interindividual factors such as sex, age, and lifestyle, and intraindividual factors such as diurnal variation, type and timing of meals, physical exercise, body posture, and the sexual cycle. Therefore, whether or not changes in laboratory values are assessed as adverse events should be determined by distinguishing them as physiological changes or pathological (adverse) changes, while taking complete account of the background characteristics of the subject concerned, such as underlying disease and complications, and baseline values of the tests and/or changes unique to the subject if he/she underwent periodic laboratory tests before study participation.

Nonetheless, there may be cases where it is not appropriate to simply identify individual abnormal changes in laboratory values and determine them to be adverse events. Considering that abnormal changes in laboratory values involve the clinical background and adverse symptoms/findings in the subject concerned, it is more important to comprehensively evaluate adverse events occurring in the subject. In other words, when no diagnostic term can be defined for an adverse event, individual abnormal changes

Table 1 Criteria for assessing abnormal changes in laboratory values as adverse events

Laboratory tests	Laboratory values to be reviewed for adopting as adverse events
Red blood cell count (RBC)	Male <3,500,000/mm^3, female <3,200,000/mm^3
Hemoglobin	<10 g/dL
Hematocrit	Male <35%, female <30%
White blood cell count (WBC)	<3000/mm^3. Increased values are not determined to be adverse events unless there is some special reason. It may be handled as neutrophil count decreased (<1,500/mm^3) or lymphocytes decreased (<800/mm^3)
Eosinophil count	≥500/mm^3, or ≥10% as % of eosinophil in WBC Allergic disease should be taken into account in the subject
Platelet count	Decrease <75,000/mm^3
	Increase ≥600,000/mm^3 with some symptoms, or ≥1,000,000/mm^3
Aspartate aminotransferase (AST)	Above 2.5-fold of the upper limit of the institutional standard levels
Alanine aminotransferase (ALT)	Even if the value is not above 2.5-fold, it should be considered to be handled as an adverse event in the following cases:
γ-Glutamyl transferase (γ-GT)	
Alkaline phosphatase (ALP)	Not above 2.5-fold of the institutional standard level, but the investigational drug is likely to have greatly contributed to the change based on the range of change
Lactate dehydrogenase (LDH)	
Leucine aminopeptidase (LAP)	Not above 2.5-fold of the institutional standard level, but there was a tendency for increase during treatment, and the value had recovered at the time when there was no longer the effect of the investigational drug
Creatine kinase (CK)	
Total bilirubin	≥1.5-fold of the upper limit of the institutional standard levels
Direct bilirubin	
Serum creatinine	
Blood urea nitrogen (BUN)	
Na	Decrease ≤125 mEq/L, increase ≥155 mEq/L
K	Decrease ≤3.2 mEq/L, increase ≥5.5 mEq/L
Cl	Decrease ≤96 mEq/L, increase ≥115 mEq/L
Blood sugar (fasting)	Decrease <55 mg/dL, increase >160 mg/dL
	(For decreases, changes to <55 mg/dL are considered to be abnormal changes regardless of whether or not the subject has had a meal)
Urinary sugar/protein	Changes of ≥2 steps as qualitative value (−, ±, +, ++, etc.) (when ± is included in a qualitative value, ± should be also counted as a step)

in laboratory values can be handled as separate adverse events; however, it has been found to be more appropriate to put multiple related abnormal laboratory values together and consider them as a symptom or finding than to determine these abnormal values to be adverse events. When abnormal changes in laboratory values are assumed to be adverse events, it is critical to define them as related symptoms or findings in order to handle them as adverse events, as exemplified below.

For example, in addition to the terms "ALT (alanine aminotransferase) increased" and "AST (aspartate aminotransferase) increased," when multiple abnormal laboratory values related to liver function, such as "γ-GT (γ-glutamyl transferase)" and "ALP (alkaline phosphatase)," which do not exceed the ranges of laboratory values that should be handled as adverse events are noted at the same time, they should be defined as "abnormal liver function tests".

In the present assessment, we reviewed the JSC's current criteria for laboratory values in clinical studies of antimicrobial agents and we present new guidelines for assessment criteria. In the development of antimicrobial agents, it is not sufficient to only assess the presence or absence of abnormal changes in laboratory values occurring in each subject and to tabulate them to calculate the incidence of abnormal changes for each laboratory test item. It is also important to comprehensively analyze the laboratory data collected in clinical studies, using shift tables that showed changes in laboratory findings before and after administration and scatter diagrams, to evaluate safety in detail as to whether there are any laboratory test items showing characteristic changes over time for the antimicrobial agent concerned, and whether there are abnormal changes and changes over time that may lead to significant adverse reactions. In order to achieve this, it is preferable to apply the criteria as indexes that are not affected by any bias such as physicians' judgment, and to tabulate/analyze abnormal changes in laboratory values based on certain criteria regardless of determining the changes to be adverse events.

Points to consider for safety evaluation of laboratory values

The Committee has created evaluation criteria for each laboratory test item that is usually performed in clinical studies of antimicrobial agents. The laboratory test items specified in this report are not intended to be essential items, though such items should be identified and selected in consideration of the characteristics of the antimicrobial agents to be developed. In addition, we have determined that total cholesterol and blood triglycerides, for which clear categories of changes could not be presented in this review, and basophil and monocyte counts, for which the clinical significance of their changes is unknown, are not always required to be evaluated in clinical studies of antimicrobial agents, unless otherwise specified.

Based on the examination in this committee, patients with laboratory values categorized as Grade 3 or higher (Grade 4 or higher for Na and K) at baseline were found to be not suitable for safety evaluation. Therefore, in principle, such patients should be excluded from enrollment in future clinical studies. For severe hepatic dysfunction and renal impairment, which have been stipulated in the exclusion criteria, approximate laboratory values indicating which candidates should be excluded from study enrollment are presented in Table 2.

In previous clinical studies of antimicrobial agents, efficacy and safety were generally evaluated based on the results at the completion of treatment (administration). In recent years, however, concepts of test and observation schedules in clinical studies have changed so that the timing of primary efficacy evaluation is consistent with that in Western countries, such as assessing efficacy based on the results at the time of "test of cure visit" after the completion of treatment (administration). In the future, tests and observation will preferably be performed for safety evaluation at the time of "test of cure visit" after the completion of treatment (administration).

Criteria for safety evaluation of symptoms and findings

The definition of "adverse event" in clinical studies is in accordance with ICH harmonized tripartite guideline "Clinical safety data management: definitions and standards for expedited reporting" [5]. Any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, has to be noted. Therefore, when identifying such symptoms or findings, all of them should be handled as adverse events, and their severity and causal relationship with the product should be assessed.

In clinical studies of antimicrobial agents, the terms "diarrhea" and "loose stools" occur relatively frequently. Consequently, the evaluation of "diarrhea" and "loose stools" in a uniform manner is important for comparing drugs; thus, these events should be assessed based on the criteria below.

Evaluation of "diarrhea" and "loose stool"

We defined "diarrhea" and "loose stool" using the *Criteria for assessment of antimicrobial agents in pediatric clinical study* [6] as a reference to be able to apply the definitions to clinical studies mainly in adults. "Diarrhea" and "loose stool" should be identified and assessed based on the definition listed in Table 3.

Severity assessment

Common assessment criteria for the severity of all adverse events are as shown in Table 4. The assessment of seriousness should be made as specified in the "Clinical safety data management: definitions and standards for expedited reporting" [5].

Assessment of a causal relationship

The assessment of a causal relationship is particularly important information regarding an adverse event.

Currently, typical categories used for the assessment of a causal relationship in clinical studies often include several ranks (e.g., "related," "probably related", "possibly related", and "not related"). In the present criteria

Table 2 Approximate laboratory values for severe hepatic dysfunction and renal impairment

Item		Approximate laboratory values for exclusion criteria
Liver function	AST, ALT, ALP, γ-GT, LDH, and LAP	Above 5-fold of the upper limit of the institutional standard levels
	Total bilirubin and direct bilirubin	Above 2-fold of the upper limit of the institutional standard levels
Renal function	Serum creatinine and BUN	

Table 3 Definitions of "diarrhea" and "loose stool"

Normal stool		Stool having a smooth surface and a shape similar to sausage
		Stool having clear margins, being soft and semisolid and having a shape like a coiled snake
Loose stool		Thick stool without a shape like a coiled snake
Diarrhea		
Muddy stool		Muddy stool without margins and shape
Watery stool		Watery stool without lumps

Table 4 Assessment of the severity of adverse events

Severity	Criteria
Mild	An event that does not interfere with activities of daily living (when abnormal changes in laboratory values are evaluated individually) e.g., abnormal changes in laboratory values without adverse symptoms correspond to this criterion
Moderate	An event that interferes with activities of daily living, including the case where the investigational treatment is discontinued. When the treatment has been terminated by a patient's judgment, the event should be assessed while taking account of the symptom or finding concerned and the patient's condition (when abnormal changes in laboratory values are evaluated individually), e.g., abnormal changes in laboratory values which need follow-up examination and also treatment, or which accompany adverse symptoms interfering with activities of daily living
Severe	An event that prevents activities of daily living, those events which do not meet the above criteria for mild and moderate events

When the concerned symptom or finding is present at baseline and has worsened, and it is assessed as an adverse event, its severity should not be determined based on a difference in the condition from baseline but based on the condition at the time when the case is judged to be an adverse event

When disease (including suspected disease) can be identified based on multiple related abnormal changes in laboratory values and the events are defined as other related disease, it should not be automatically determined to be "severe," but the severity of the concerned disease should be comprehensively assessed

for safety evaluation of antimicrobial agents, a two-category assessment is recommended, from the global perspective, and an assessment method is shown in Table 5. In this Table, examples of "Information useful for assessing the relationship" are presented. They should be used as a reference for the assessment of a causal relationship.

In some cases, a causal relationship is classified into several categories at an early development stage. The causal relationship can be evaluated by subdividing the category of "related" specified here. In such cases, those adverse events whose causal relationships are categorized as so-called "unlikely" should be evaluated as adverse reactions.

Conclusions

As mentioned at the beginning, we (the Committee) have created criteria for the safety evaluation of antimicrobial agents from the global viewpoint, taking into consideration consistency with Western safety evaluation criteria. Therefore, we should pay attention when adopting these criteria after the development of a new antimicrobial agent has been started. This is because there may be some inconsistencies when comparing results using other these criteria and the JSC's current criteria, such as those related to liver function. For instance, in the case where the safety evaluation is made according to the JSC's current criteria in a phase II clinical study, and the present criteria are adopted from a phase III study, it is important to establish an analysis plan which enables the safety assessment to be compared and analyzed based on both sets of criteria, and to fully examine the appropriateness of switching the assessment criteria in the middle of drug development based on the results.

It is also critical to compare drugs based not only on the safety assessment of the individual antimicrobial agents but also based on unified assessment using the present criteria. We hope that the present criteria will be widely employed when conducting clinical studies of antimicrobial agents so that the present criteria can be re-evaluated and the necessity for their amendment in the future can be examined.

Adverse events that are likely to occur in clinical studies of antimicrobial agents

We analyzed adverse events occurring in clinical studies of antimicrobial agents (3 drugs from 3 companies) based on the system organ class and preferred term of Medical dictionary for regulatory activities terminology (MedDRA) J/V9.0.

Table 5 Criteria for assessment of a causal relationship

Causal relationship	Criteria
Related	The adverse event whose relationship to the investigational agent is temporally appropriate can be explained as a known reaction or pharmacological action of the investigational drug or its analogue
	Factors other than the investigational drug (e.g., primary disease, underlying disease, complication, and concomitant medication) should be fully examined. The causal relationship to the investigational drug should be determined as "related" unless the relationship is definite
Not related	The concerned adverse event is determined to be not late-onset, and a relationship between the investigational treatment and adverse event is temporally inappropriate
	The event is caused by factors other than the investigational drug (e.g., primary disease, underlying disease, complication, and concomitant medication), and the relationship to the investigational drug can be almost certainly or completely denied
Information useful for assessing the relationship	
Adverse event occurred	
Presence or absence of overdosing or long-term treatment	
Whether the drug was administered prior to the onset of adverse event	
Presence or absence of concomitant medications or previous treatment drugs	
Presence or absence of local reaction (e.g., use of injection, suppository, and sublingual formulations)	
Whether the event disappeared after treatment discontinuation	
Whether concomitant medications were discontinued at the same time	
Past history	
Whether a similar event occurred in the past (regardless of drug treatment)	
Whether the event is associated with drugs in the same class	
Whether the event is associated with drugs in other classes	
Findings	
Whether the temporal interval between drug administration and the onset of the event is appropriate	
Whether the concerned event occurs spontaneously in rare cases	
Whether the event has been known to possibly occur in relation to treated disease or existing illness	
Whether the concerned event tends to develop in relation to treated disease or concurrent illness	
Whether non-drug treatment is associated (e.g., puncture and surgery)	
Whether there are any other associated factors (e.g., alcohol consumption, other habits, and environment)	
Whether the concerned event has been found in past clinical studies or in drugs in the same class	
Whether the concerned event can be explained based on the biological properties of the investigational drug or drugs in the same class	
Whether the concerned event has been reported for pharmacologically similar drugs	
Whether the concerned event has been reported for concomitant medications or previous treatment drugs	
Whether the concerned event is possibly caused by drug interaction	

Table 6 Types and numbers of adverse events that have occurred in clinical studies of antimicrobial agents (MedDRA J/V9.0)

System organ class	No. of types
Gastrointestinal disorders	40
Respiratory, thoracic, and mediastinal disorders	22
Skin and subcutaneous tissue disorders	21
General disorders and administration-site conditions	16
Infections and infestations	15
Musculoskeletal and connective tissue disorders	15
Nervous system disorders	14
Injury, poisoning, and procedural complications	9
Psychiatric disorders	8
Renal and urinary disorders	8
Eye disorders	6
Cardiac disorders	6
Ear and labyrinth disorders	5
Vascular disorders	4
Blood and lymphatic system disorders	3
Reproductive system and breast disorders	3
Metabolism and nutrition disorders	2
Immune system disorders	1

Table 7 Adverse events that have occurred in clinical studies of antimicrobial agents (MedDRA J/V9.0)

System organ class	Code	Preferred term
Infections and infestations	10022000	Influenza
	10001076	Acute sinusitis
	10019948	Herpes simplex
	10019974	Herpes zoster
	10020377	Hordeolum
	10028810	Nasopharyngitis
	10034835	Pharyngitis
	10035664	Pneumonia
	10043873	Tinea pedis
	10044008	Tonsillitis
	10046306	Upper respiratory tract infection
	10046898	Vaginal candidiasis
	10060889	Tinea infection
	10062352	Respiratory tract infection
	10009899	Pseudomembranous colitis
Blood and lymphatic system disorders	10013442	Disseminated intravascular coagulation
	10025188	Lymphadenitis
	10025197	Lymphadenopathy
Immune system disorders	10002817	Antiphospholipid syndrome

Table 7 continued

System organ class	Code	Preferred term
Metabolism and nutrition disorders	10002646	Anorexia
	10061428	Decreased appetite
Psychiatric disorders	10002855	Anxiety
	10012378	Depression
	10010893	Conversion disorder
	10022437	Insomnia
	10029333	Neurosis
	10054196	Affect lability
	10038743	Restlessness
	10061284	Mental disorder
Nervous system disorders	10008118	Cerebral infarction
	10013496	Disturbance in attention
	10013573	Dizziness
	10013578	Dizziness postural
	10013887	Dysarthria
	10013911	Dysgeusia
	10019211	Headache
	10020937	Hypoesthesia
	10033775	Paresthesia
	10034701	Peroneal nerve palsy
	10021118	Hypotonia
	10041349	Somnolence
	10042772	Syncope
	10044565	Tremor
Eye disorders	10000173	Abnormal sensation in eye
	10015993	Eyelid edema
	10047513	Vision blurred
	10064132	Conjunctivochalasis
	10007739	Cataract
	10030041	Ocular hyperemia
Ear and labyrinth disorders	10011878	Deafness
	10043882	Tinnitus
	10047348	Vertigo positional
	10052137	Ear discomfort
Cardiac disorders	10011703	Cyanosis
	10033557	Palpitations
	10040752	Sinus tachycardia
	10003658	Atrial fibrillation
	10007554	Cardiac failure
	10015856	Extrasystoles
Vascular disorders	10016825	Flushing
	10033546	Pallor
	10040560	Shock
	10020772	Hypertension
	10060800	Hot flush

Table 7 continued

System organ class	Code	Preferred term
Respiratory, thoracic, and mediastinal disorders	10003553	Asthma
	10011224	Cough
	10013968	Dyspnea
	10014962	Eosinophilic pneumonia
	10015090	Epistaxis
	10018964	Hemoptysis
	10022611	Interstitial lung disease
	10028735	Nasal congestion
	10034844	Pharyngolaryngeal pain
	10035598	Pleural effusion
	10035759	Pneumothorax
	10036790	Productive cough
	10037383	Pulmonary fibrosis
	10037410	Pulmonary infarction
	10037423	Pulmonary edema
	10038695	Respiratory failure
	10039085	Rhinitis allergic
	10039101	Rhinorrhea
	10041232	Sneezing
	10057009	Pharyngeal erythema
	10061877	Obstructive airways disorder
	10068319	Oropharyngeal pain
Skin and subcutaneous tissue disorders	10000496	Acne
	10009866	Cold sweat
	10011985	Decubitus ulcer
	10012431	Dermatitis
	10012442	Dermatitis contact
	10013687	Drug eruption
	10014184	Eczema
	10014190	Eczema asteatotic
	10015150	Erythema
	10019343	Heat rash
	10020642	Hyperhidrosis
	10033551	Palmar erythema
	10034972	Photosensitivity reaction
	10037087	Pruritus
	10037549	Purpura
	10037844	Rash
	10037868	Rash maculo-papular
	10037876	Rash papular
	10039793	Seborrheic dermatitis
	10046735	Urticaria
	10052576	Pruritus generalized

Table 7 continued

System organ class	Code	Preferred term
Gastrointestinal disorders	10000059	Abdominal discomfort
	10000060	Abdominal distension
	10000081	Abdominal pain
	10000084	Abdominal pain lower
	10000087	Abdominal pain upper
	10000097	Abdominal tenderness
	10008417	Cheilitis
	10010774	Constipation
	10012735	Diarrhea
	10013781	Dry mouth
	10013946	Dyspepsia
	10016101	Feces hard
	10016766	Flatulence
	10017367	Frequent bowel movements
	10017853	Gastritis
	10017944	Gastrointestinal disorder
	10018286	Gingival pain
	10018292	Gingivitis
	10018386	Glossitis
	10018388	Glossodynia
	10018836	Hematochezia
	10027141	Melena
	10020601	Hyperchlorhydria
	10023003	Irritable bowel syndrome
	10024552	Lip dry
	10028813	Nausea
	10030973	Oral discomfort
	10031009	Oral pain
	10034023	Parotid gland enlargement
	10039408	Salivary gland enlargement
	10039424	Salivary hypersecretion
	10042101	Stomach discomfort
	10042128	Stomatitis
	10043951	Tongue disorder
	10047700	Vomiting
	10051992	Lip erosion
	10053155	Epigastric discomfort
	10056819	Gastric disorder
	10057371	Hypoesthesia oral
	10057372	Paresthesia oral

Table 7 continued

System organ class	Code	Preferred term
Musculoskeletal and connective tissue disorders	10003239	Arthralgia
	10003988	Back pain
	10006811	Bursitis
	10008690	Chondrocalcinosis pyrophosphate
	10016717	Fistula
	10016750	Flank pain
	10028334	Muscle spasms
	10028372	Muscular weakness
	10028411	Myalgia
	10028836	Neck pain
	10033425	Pain in extremity
	10040617	Shoulder pain
	10049816	Muscle tightness
	10052904	Musculoskeletal stiffness
	10061224	Limb discomfort
Renal and urinary disorders	10011730	Cylindruria
	10013990	Dysuria
	10018867	Hematuria
	10036018	Pollakiuria
	10038435	Renal failure
	10046543	Urinary incontinence
	10049710	Urethral hemorrhage
	10060695	Residual urine
Reproductive system and breast disorders	10004073	Balanitis
	10027304	Menopausal symptoms
	10037093	Pruritus genital
General disorders and administration-site conditions	10003549	Asthenia
	10008469	Chest discomfort
	10008479	Chest pain
	10008531	Chills
	10011906	Death
	10016322	Feeling abnormal
	10016334	Feeling hot
	10017577	Gait disturbance
	10022067	Injection-site hemorrhage
	10022086	Injection-site pain
	10022090	Injection-site phlebitis
	10025482	Malaise
	10030124	Edema peripheral
	10034568	Peripheral coldness
	10037660	Pyrexia
	10043458	Thirst

Table 7 continued

System organ class	Code	Preferred term
Injury, poisoning, and procedural complications	10003986	Back injury
	10016173	Fall
	10023229	Joint sprain
	10037765	Radiation pneumonitis
	10039117	Rib fracture
	10041569	Spinal fracture
	10049796	Excoriation
	10049947	Lumbar vertebral fracture
	10050584	Contusion

As shown in Table 6, in the clinical studies of antimicrobial agents, events related to "gastrointestinal disorders" are most frequently followed by "respiratory, thoracic and mediastinal disorders," "skin and subcutaneous tissue disorders," "general disorders and administration site conditions," "infections and infestations," "musculoskeletal and connective tissue disorders", and "nervous system disorders".

Individual adverse events that occurred in clinical studies of antimicrobial agents are shown in Table 7.

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