On-going Activities at Safety Analytics and Package Insert in Japan

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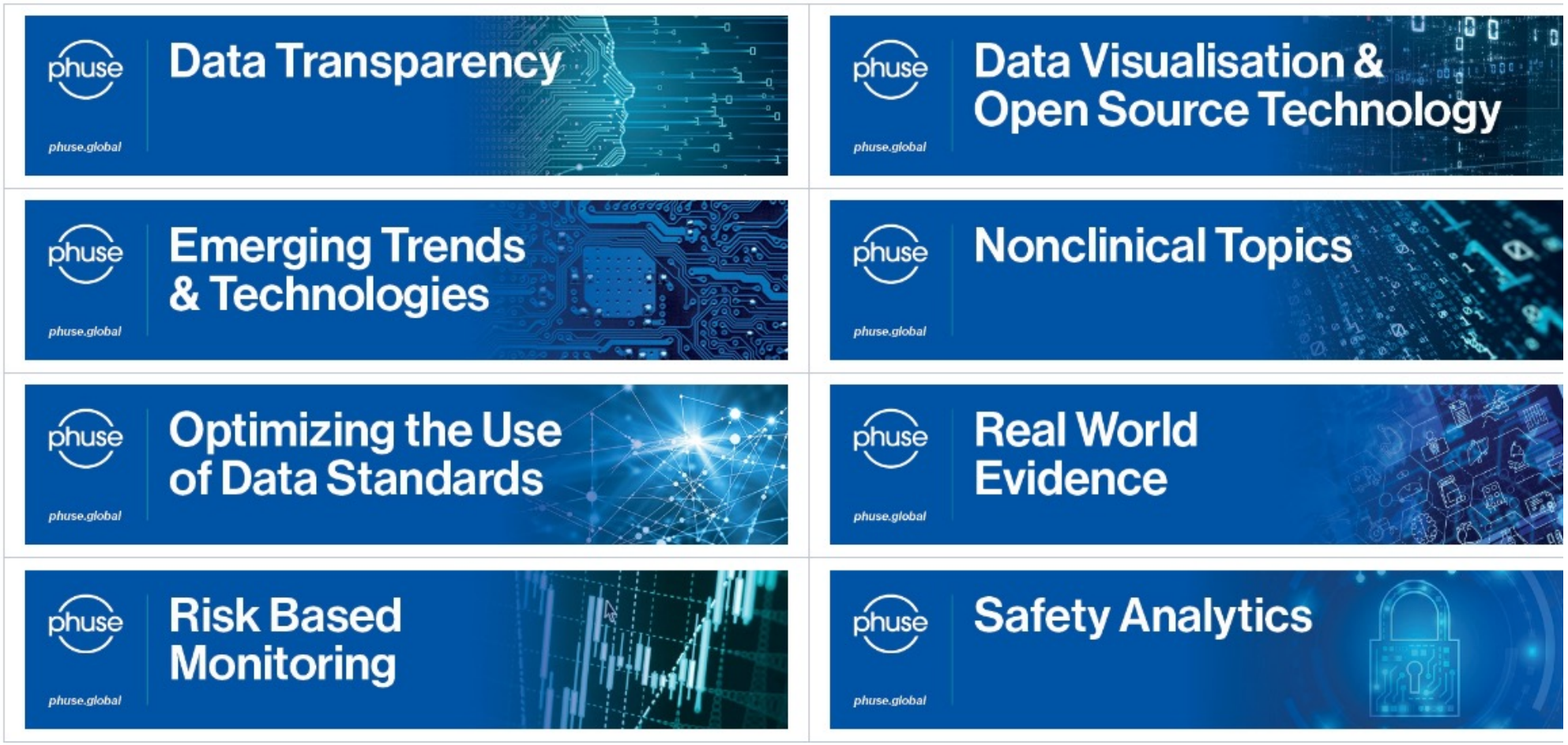
@PHUSE Japan SDE 2023, 08-Dec-2023

Outlines

- Overview of PHUSE Working Group and Safety Analytics
- Recent Example of Package Insert
  - Definition of Adverse Drug Reactions
  - MedDRA Preferred Term Aggregation
- On-going Discussions from Safety Analytics, PHUSE
  - Adverse Event Collection Recommendations
  - Adverse Event Grouping in Safety
- Summary

Background – Working Groups Today



Recent example from Lecanemab (1)

Package Insert

2023年9月作成（第1版）

日本標準商品分類番号
87119

貯　　法：2～8℃で保存
有効期間：18ヵ月

	点滴静注200mg	点滴静注500mg
承認番号	30500AMX00272000	30500AMX00273000
販売開始	－	－

ヒト化抗ヒト可溶性アミロイドβ凝集体モノクローナル抗体
レカネマブ（遺伝子組換え）製剤

生物由来製品
劇薬
処方箋医薬品注）

レケンビ®点滴静注200mg
レケンビ®点滴静注500mg

LEQEMBI® for Intravenous Infusion　　最適使用推進ガイドライン対象品目

注）注意－医師等の処方箋により使用すること

11.2 その他の副作用

	1%以上	0.5～1%未満	0.5%未満
過敏症	過敏症	皮疹	紅斑
消化器			悪心
肝臓			ALT増加

	1%以上	0.5～1%未満	0.5%未満
精神神経系	頭痛		めまい、平衡障害、錯乱状態、抑うつ症状、記憶障害、緊張性頭痛
一般・全身症状		倦怠感	起立性低血圧
筋骨格系			転倒
その他		注射部位反応	血中コレステロール増加、蛋白尿、注射部位血管外漏出

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 Infusion reaction（26.1%）

頭痛、悪寒、発熱、吐き気、嘔吐等の症状があらわれることがある。徴候や症状を注意深く観察し、異常が認められた場合は、必要に応じて本剤の注入速度を下げるか、注入を中断又は中止し適切な処置を行うこと。Infusion reactionがあらわれた場合は、次回以降の投与に際し、抗ヒスタミン薬、アセトアミノフェン、非ステロイド系抗炎症薬、副腎皮質ステロイドの予防的投与も考慮すること。

11.1.2 アミロイド関連画像異常（ARIA）

ARIA-EとしてARIA-浮腫/滲出液貯留（12.6%）、ARIA-HとしてARIA-微小出血及びヘモジデリン沈着（13.6%）、脳表ヘモジデリン沈着症（5.2%）、脳出血（0.4%）があらわれることがある。[1.2、7.1、8.1参照]

(1) ARIAは臨床症状を伴わないことが多いが、痙攣やてんかん重積等の重篤な事象が起こることがある。ARIAに関連する症状としては、頭痛、錯乱、視覚障害、めまい、吐き気、歩行障害等が報告されている。

(2) ARIAは再発することがあるため、投与を再開した場合は、注意深く患者の状態を観察するとともに、定期的なMRI検査の実施を検討すること。

(3) ARIAが再発した患者において、本剤の投与を再開した経験は限られている。

3_11904A5A1025_1_01 (pmda.go.jp)

Recent example from Lecanemab (2)

Package Insert

2023年9月作成（第1版）

日本標準商品分類番号
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貯　　法：2～8℃で保存
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販売開始	–	–

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注）注意－医師等の処方箋により使用すること

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国際共同第Ⅱ相試験（201試験）

10mg/kg隔週投与群で発現した主な有害事象（発現率5%以上かつプラセボ群より高頻度）は、注入に伴う反応（19.9%）、頭痛（13.7%）、ARIA-E（9.9%）、咳嗽（8.7%）、下痢（8.1%）、浮動性めまい（7.5%）、脳微小出血（5.6%）であった[7),8)]。

Major adverse events (with proportion >= 5% and higher proportion than placebo group)

Infusion related reaction

17.1.2 国際共同第Ⅲ相試験（301試験）

本剤群で発現した主な副作用（発現率1%以上）は、注入に伴う反応（26.1%）、ARIA-H（16.5%）、ARIA-E（12.6%）、頭痛（1.8%）、過敏症（1.7%）であった。
本剤群における症候性ARIA-E、ARIA-Hの有害事象発現率はそれぞれ2.8%、1.4%であった[1),2)]。[5.4、8.1.1参照]

Major adverse drug reactions (with proportion >= 1%)

170033_11904A5A1025_1_01 (pmda.go.jp)

Recent example from Lecanemab (3)

- ADR for lecanemab PI is defined as TEAE related to study drug from the phase 3 study (Section 11).
- Relationship to study drug was judged by investigators according to the study protocol (NEJM Christopher et al., 2023).
- Both of “infusion related reaction” and ARIA are an aggregated term with MedDRA PTs and other safety assessments, if applicable.

Discussion points

- Definition of ADR, Adverse Drug Reactions
- Grouping Adverse Event Terms

Regulation on J-Package Insert

医療用医薬品の電子化された添付文書の記載要領について

(薬生発 0611 第１号, 令和3年6月11日)

(1) 医薬品の使用に伴って生じる副作用を記載すること。

(2) 副作用の発現頻度を～臨床試験等の結果に基づいて記載すること。

000241061.pdf (pmda.go.jp)

11. 副作用

(1) 医薬品の使用に伴って生じる副作用を記載すること。

(2) 副作用の発現頻度を、精密かつ客観的に行われた臨床試験等の結果に基づいて記載すること。

(3)「11.1 重大な副作用」の記載に当たっては次の点に注意すること。

①副作用の転帰や重篤性を考慮し、特に注意を要するものを記載すること。

②副作用の事象名を項目名とし、初期症状（臨床検査値の異常を含む。）、発現機序、発生までの期間、リスク要因、防止策、特別な処置方法等が判明している場合には、必要に応じて記載すること。

③海外のみで知られている重大な副作用についても、必要に応じて記載すること。

④類薬で知られている重大な副作用については、同様の注意が必要と考えられる場合に限り記載すること。

(4)「11.2 その他の副作用」の記載に当たっては次の点に注意すること。

①発現部位別、投与方法別、薬理学的作用機序、発現機序別等に分類し、発現頻度の区分とともに記載すること。

②海外のみで知られているその他の副作用についても、必要に応じて記載すること。

Definition of ADR

独立行政法人医薬品医療機器総合機構法
平成14年法律第192号、最終改正：令和元年12月4日法律第63号

- 第４条10項
- この法律において「許可医薬品等の副作用」とは、許可医薬品又は許可再生医療等製品（中略）が適正な使用目的に従い適正に使用された場合においてもその許可医薬品又は副作用救済給付に係る許可再生医療等製品により人に発現する有害な反応をいう。

Definition of ADR

治験中に得られる安全性情報の取り扱いについて(平成7年3月20日 薬審第227号)

000156127.pdf (pmda.go.jp)

- 副作用（Adverse Drug Reaction）
  - 病気の予防，診断もしくは治療，または生理機能を変える目的で投与された（投与量にかかわらない）医薬品に対する反応のうち，有害で意図しないもの。
    医薬品に対する反応とは，有害事象のうち当該医薬品との因果関係が否定できないものを言う。
  - In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. (ICH E2A, 1994)

Product-event "Relationship"

Evidence from Individual Cases	Evidence from Multiple Cases	Previous Knowledge of AE or Drug/Class, Including Metabolites
• Positive rechallenge • Definitive (i.e., clearly defined, well documented specific case histories) • Time to onset plausible • Positive dechallenge • Lack of confounding risk factors • Amount and duration of exposure consistent/plausible with cause and effect • Corroboration of the accuracy of the case history • Case clear-cut, easily evaluated • Co-medication unlikely to play a role • Investigator's causality assessment • Lack of alternative explanation	• Positive outcome in targeted safety study(ies) • Consistently higher incidence vs placebo or active comparator (whether • statistically significant or not) • Positive dose-response (fixed or escalating dose studies) • Higher incidence vs comparator(s) of event-specific patient discontinuations • Earlier onset and/or greater severity in active vs comparator group(s) • Consistency of pattern of presenting symptoms • Consistency of time to onset • Consistent trends across studies • Consistent pattern of clinical presentation and latency	• Recognized consequence of overdose • Rarity of event in comparable untreated populations or indications • Event is commonly drug-related (e.g., neutropenia, Stevens-Johnson Syndrome) • Pharmacokinetic evidence (e.g., interactions) Known mechanism • Recognized class effect • Similar findings in animal or in vitro models • Closeness of drug characteristics to those of other drugs known to cause the AE

CIOMS VI Working Group (2005)

Definition of ADR

N Engl J Med 2023; 388:9-21
レケンビ総合製品情報概要（LEQ1001ASG）

- TEAE vs TEAE related to drug

Lecanemab (N=898)	TEAE	ADR, TEAE related to drug
Any adverse event	798 (88.9)	401 (44.7)
Infusion-related reaction	237 (26.4)	234 (26.1)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	122 (13.6)
ARIA-E	113 (12.6)	113 (12.6)
Headache	100 (11.1)	16 (1.8)

- Is investigator-assessed relationship appropriate for defining ADR?

Definition of ADR

N Engl J Med 2023; 388:9-21
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Headache	100 (11.1)	16 (1.8)

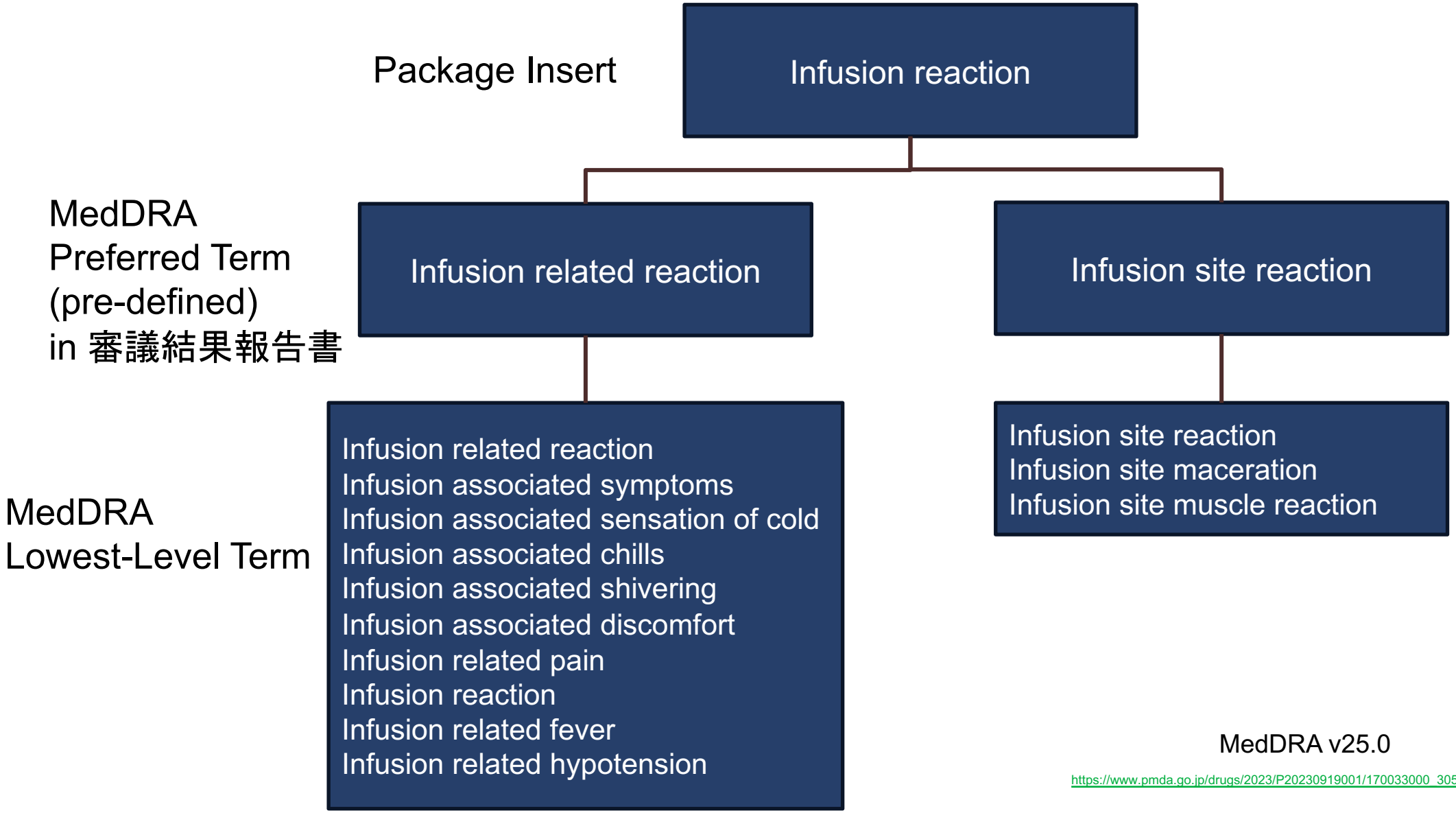
TEAE	Lecanemab (N=898)	Placebo (N=897)
Headache	100 (11.1)	73 (8.1)

- Where events are common and occur in multiple patients in controlled trials, it is usually not necessary or helpful to consider each case individually. Rather, all reported cases can be considered potentially drug-related, and causality is assessed by comparing the rates of reports in patients treated with test drug and in control groups (FDA Reviewer's Guidance, 2005).
- Be mindful of Common Pitfall: Believing ADR determination is based on statistical criteria.

Definition of ADR

- White Paper for “Adverse Event Collection” is under development and it discusses a value of that the investigator assessment of relationship for non-serious adverse events. The group has been communicating with several stakeholders who are using the assessment.
- White Paper will be released for public review soon.

Aggregated Terms



MedDRA v25.0

https://www.pmda.go.jp/drugs/2023/P20230919001/170033000_30500AMX00272_A102_1.pdf

Pre-defined Preferred Terms

MedDRA v25.0 obtains 82 Preferred Terms [link to 190 LLTs] starting with “Injection site.”

- Need a **rationale of selecting** 2 PTs, “Injection site reaction” and “Injection related reaction,” for “Injection reaction.”
- May require additional efforts and a plan while/about **MedDRA coding** at Data Manager site.
- Need confirmation about **thoroughness**.
- Need consideration for the **version up**.

PT with “Injection site”	#LLT1
Injection site abscess	2
Injection site abscess sterile	1
Injection site alopecia	1
Injection site anaesthesia	4
Injection site atrophy	6
Injection site bruising	1
Injection site calcification	1
Injection site cellulitis	1
Injection site coldness	1
Injection site cyst	2
Injection site deformation	1
Injection site dermatitis	1
Injection site discharge	1
Injection site discolouration	7
Injection site discomfort	2
Injection site dryness	1
Injection site dysaesthesia	2
Injection site eczema	1
Injection site erosion	2
Injection site erythema	5
Injection site exfoliation	3
Injection site extravasation	4
Injection site fibrosis	2
Injection site granuloma	2
Injection site haematoma	4
Injection site haemorrhage	9
Injection site hyperaesthesia	2
Injection site hypersensitivity	3
Injection site hypertrichosis	1
Injection site hypertrophy	2
Injection site hypoaesthesia	6
Injection site indentation	1
Injection site induration	3
Injection site infection	2
Injection site inflammation	5
Injection site injury	2
Injection site irritation	1
Injection site ischaemia	2
Injection site joint discomfort	1
Injection site joint effusion	2
Injection site joint erythema	2
Injection site joint infection	1

PT with “Injection site”	#LLT1
Injection site joint inflammation	3
Injection site joint movement impairment	1
Injection site joint pain	2
Injection site joint swelling	1
Injection site joint warmth	1
Injection site laceration	1
Injection site lymphadenopathy	2
Injection site macule	1
Injection site mass	4
Injection site movement impairment	1
Injection site muscle atrophy	1
Injection site muscle weakness	1
Injection site necrosis	3
Injection site nerve damage	1
Injection site nodule	2
Injection site oedema	4
Injection site pain	9
Injection site pallor	1
Injection site panniculitis	1
Injection site papule	1
Injection site paraesthesia	4
Injection site phlebitis	2
Injection site photosensitivity reaction	1
Injection site plaque	1
Injection site pruritus	2
Injection site pustule	1
Injection site rash	4
Injection site reaction	7
Injection site recall reaction	1
Injection site scab	2
Injection site scar	2
Injection site streaking	1
Injection site swelling	2
Injection site telangiectasia	1
Injection site thrombosis	3
Injection site ulcer	2
Injection site urticaria	4
Injection site vasculitis	1
Injection site vesicles	4
Injection site warmth	1

AE Groupings in Safety (AEGiS)

AEGiS Objectives

Objectives of the AEGiS Project Team Include:

- Define best practices for utilization of AE groupings
- Develop points to consider/recommendations on implementation of AE groupings
- Recommend efficient standardized processes and introduce ways to leverage new technologies

PowerPoint Presentation (phuse.s3.eu-central-1.amazonaws.com)

AE Groupings in Safety (AEGiS)

Groupings Included in AEGiS Project

FDA Medical Queries:

- 104 FMQs, 4 of which also have an algorithmic component
- Each grouping represents a medical concept
- Goal to improve safety signal detection in clinical trial data
- FMQs include AE terms without regard to causality including those with presumably non-drug-related causes
- Includes non-PTs, former PTs, and other terminologies

Standardized MedDRA Queries:

- ~110 SMQs with standardized medical terminology used broadly across industry
- Validated and maintained groupings for safety topics of interest
- Hierarchy includes focused 'Sub-SMQs' for ~25% of topics

Sponsor Developed or Custom Groupings

https://healthpolicy.duke.edu/events/advancing-premarket-safety-analytics
www.meddra.org

PowerPoint Presentation (phuse.s3.eu-central-1.amazonaws.com)

Summary

- ADRs are shown in Japan PI.
- Definition of ADR may vary depending on MAH, but “AE related to drug” is a common practice.
- MedDRA PT serves as AE term for clinical studies, but aggregated term is likely used in PI
- PHUSE WG titled “Adverse Event Collection Recommendations” is discussing future to-be of “relatedness” by investigators.
- PHUSE WG titled “AE Groupings in Safety” is preparing a white paper to communicate a best practice and points to be considered for aggregated event terms.

Abbreviations:
ADR=Adverse Drug Reaction, PI=Package Insert, MAH=Market Authorization Holder, AE=Adverse Event, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, WG=Working Group

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Thank you