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Report on Investigation Results

October 23, 2020

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Lidocaine hydrochloride/adrenaline injections
[Branded name]	See Appendix 1.
[Indications]	See Appendix 1.
[Dosage and administration]	See Appendix 1.
[Approval holder]	Aspen Japan K.K.
[Investigating office]	Office of Pharmacovigilance I

Pharmaceuticals and Medical Devices Agency

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II. Investigation background

Lidocaine hydrochloride/adrenaline injections (excluding preparations for dental use) (hereinafter referred to as “this drug”) was approved in Japan in February 1956.

The current package insert specifies patients for whom anaesthesia is intended for “ears, digits, or penis [A necrotic condition may occur]” as a contraindication of this drug under the “Conduction/infiltration anaesthesia,” Contraindication section.

On January 27, 2020, the Oto-Rhino-Laryngological Society of Japan submitted a written request to the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as the “Safety Division”) asking that the package insert of this drug be revised to allow the use in conduction and infiltration anaesthesia in patients for whom anaesthesia is intended for ears for the following reasons:

- (1) No literature published in Japan or other countries has been identified that report a necrotic condition resulting from vascular insufficiency caused by vasoconstrictive action of adrenaline following administration of this drug to the ears.
- (2) The ear is surrounded by abundant blood flow at its upper, lower, right, and left sides.¹
- (3) In clinical practice, adrenaline is used for prolonging the duration of local anaesthesia and reducing bleeding in the operative field.
- (4) Standard textbooks recommend the use of adrenalin-containing local anaesthetics.

In addition, on February 10, 2020, the Japanese Society for Surgery of the Hand (hereinafter referred to as “JSSH”) submitted a written request to the Safety Division asking that the package insert be revised to allow the use in conduction and infiltration anaesthesia in patients for whom anaesthesia is intended for hands for the following reasons:

- (1) A large scale study found no complications such as necrosis of fingers following the administration of this drug.
- (2) The guidelines by the American Academy of Dermatology recommend the use of this drug for subcutaneous infiltration anaesthesia of the fingers with the recommendation strength A².

¹ An annexed document was submitted as the literature studying the auricles of 8 patients that confirmed a communication between the upper branch of superficial temporal artery and that of posterior auricular artery in the upper third of the helical rim and a communication between the upper and lower branches of superficial temporal artery in the entire helical rim (Reevaluation of the arterial blood supply of the auricle. (J Anat. 2017; 230: 315-24)).

² Recommendation strength A: Recommended based on consistent, strong evidences.

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- (3) Since no tourniquet is used for obtaining a bloodless field during a surgery using this drug, the surgeon does not need to exercise caution for any pain or neuropathy caused by a tourniquet, or accumulated haematoma, blood flow disorder, or wound scar after the release of the tourniquet.
- (4) Since this drug anaesthetizes the sensory nerves of fingers alone, the movement of the affected fingers can be maintained during the surgery.³

Furthermore, on April 17, 2020, the Japanese Society for Surgery of the Foot (hereinafter referred to as “JSSF”) submitted a written request to the Safety Division asking that the package insert be revised to allow the use of the drug in conduction and infiltration anaesthesia in patients for whom anaesthesia is intended for toes, considering that the dose of anaesthetic agent will be decreased and the risk of anaesthetic poisoning will be reduced in elderly patients and those with small body size by the use of this drug with its enhanced analgesic effect and prolonged duration of effect.

No written request has been submitted by academic societies or other relevant parties asking for the lifting of contraindication for the penis.

On August 6, 2020, the Safety Division requested the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) to conduct an investigation to evaluate the appropriateness to lift the contraindications of this drug for conduction and infiltration anaesthesia of ears or digits. PMDA accordingly conducted the requested investigation and evaluated the proposed revision of the package insert of this drug.

During the investigation, the PMDA held an Expert Discussions. The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. PMDA’s investigation

1. Background of contraindications noted in package insert of this drug

PMDA made inquiries to the approval holder about the reasons for listing the contraindication in the current package insert, to which the approval holder submitted a response explaining the background of the current listing.

In 1971, a statement was added to the Precautions sections that preparations not containing vasoconstrictor should be used for anaesthesia of ears, fingers, toes, or penis.

³ Dosage of Local Anesthesia in Wide Awake Hand Surgery (J Hand Surg Am. 2013; 38: 2025-8)

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The MAH could not identify how the addition of the statement was decided. Subsequently in 1976 when the format of the Precautions sections was changed, “anaesthesia of ears, fingers, toes, or penis” was added to the “Methods of anaesthesia: Conduction/infiltration anaesthesia” under the “This drug should not be administered to the following patients” section, which was then equivalent to the current Contraindications section. In 1995, the language “a necrotic condition may occur” was added. Reasons for the changes in the description could not be identified.

Changes in package insert⁴

1956	<p>Dosage and administration</p> <p>Generally, Xylocaine Injection with Epinephrine is used. The maximum daily dose is 0.5 g as lidocaine hydrochloride.</p> <p>Xylocaine Injection products that do not contain epinephrine are used mainly in patients with hypersensitivity to epinephrine, especially those with symptoms that may be adversely affected by epinephrine such as thyrotoxicosis, vasospasm, arteriosclerosis, and diabetes mellitus, or for anaesthesia of digits and penis, or anaesthesia during a very simple surgery.</p>
1971	<p><Precautions></p> <p>When this drug is used for anaesthesia of ears, digits, or penis, a preparation not containing vasoconstrictor should be used.</p>
1976	<p><Precautions></p> <p>2. This drug should not be administered to the following patients: (7) Patients for whom anaesthesia is intended for ears, digits, or penis.</p>
1995	<p><Precautions></p> <p>2. Contraindications (This drug should not be administered to the following patients or sites:). (7) Anaesthesia of ears, digits, or penis (A necrotic condition may occur.)</p>
2000	<p>Methods of anaesthesia: Conduction/infiltration anaesthesia</p> <p>Contraindications (This drug should not be administered to the following patients:)</p> <p>Patients for whom anaesthesia is intended for ears, digits, or penis (A necrotic condition may occur.)</p>

⁴ Excerpt from the response by the approval holder

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2. Description related to this drug in guidelines published in Japan or other countries, package inserts in other countries, published literature, and standard textbooks used in Japan and other countries

2.1 Guidelines

2.1.1 Clinical guidelines for anaesthetics and anaesthesia-related drugs, version 3 revision 4 (by the Japanese Society of Anesthesiologists; hereinafter referred to as the “Japanese guidelines”)⁵

The guidelines state that local anaesthetics containing adrenaline should not be used for ears, digits, or penis.

2.1.2 Guidelines for the use of local anesthesia in office-based dermatologic surgery (by the American Academy of Dermatology, 2016; hereinafter referred to as the “US guidelines”)⁶

The guidelines recommend the addition of adrenaline to a local anaesthetic for ears, nose, and digits as the strength of recommendation A and provide the following information:

- Multiple systematic reviews and randomized controlled trials have found the addition of adrenaline to local infiltrative anaesthesia to be safe for use in digits, hands, and feet. No cases of necrosis were reported, and the use of epinephrine resulted in less need for tourniquet plus faster onset and longer duration of anaesthesia.
- The addition of adrenaline to tumescent local anaesthesia for ear and nose reconstruction also resulted in no anaesthesia-related complications, and it led to decreased operative time and need for electrocautery hemostasis.
- Avoiding excessive injection volume, or excessive tourniquet pressure, adrenaline affords many benefits without the risk of skin necrosis.

2.2 Description in Package Inserts of Other Countries

Anaesthesia of ears and digits is described as follows in the package inserts of this drug in other countries (Appendix 2).

2.2.1 Package insert in the US

The section “Contraindications” does not refer to anaesthesia of ears and digits, but the section “Precautions” states that it should be administered with caution to areas of the body

⁵ https://anesth.or.jp/users/person/guide_line/medicine (searched on October 8, 2020)

⁶ J Am Acad Dermatol. 2016 Jun;74(6):1201-19.

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supplied by end arteries or having compromised blood supply.

2.2.2 Package insert in the UK

The section “Contraindications” states that the use of a vasoconstrictor is contraindicated for anaesthesia of fingers, toes, tip of nose, ears, and penis.

2.2.3 Package insert in Canada

The section “Contraindications” does not include a relevant description, but the section “Warning and Precautions” states that it should not be used in areas of the body supplied by end arteries, such as digits, nose, ears, or penis, or otherwise having a compromised blood supply.

2.2.4 Package insert in Australia

The section “Contraindications” indicates that it must not be used for local anaesthesia in sites of the body with compromised blood supply or supplied by end arteries, such as fingers, toes, nose, ears, or penis.

2.2.5 Package insert in Germany

The section “Contraindications (Gegenanzeigen)” states that this drug is contraindicated for anaesthesia of the terminal parts of blood vessels.

2.2.6 Package insert in France

The section “Contraindications (Contre-indications)” indicates that it is contraindicated for local infiltration anaesthesia of terminal sites (fingers and penis).

2.3 Published literature

The representative published articles discussing the use of this drug in ears, fingers, and toes are as follows:

2.3.1 Excerpt from literature investigated by PMDA⁷

2.3.1.1 Is Epinephrine Safe for Infant Digit Excision? A Retrospective Review of 402 Polydactyly Excisions in Patients Younger than 6 Months. (Plast Reconstr Surg. 2019;

⁷ Published articles in PubMed were searched for by using keywords ((lidocaine or lignocain) and (epinephrine or adrenaline) and necrosis and (fingers, toes, or ear)) (August 18, 2020). The identified articles that have an accessible abstract in English are shown after excluding animal studies and literature review.

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144: 149-54)

A review was conducted in 215 infants younger than 6 months who underwent 402 preaxial and postaxial polydactyly excisions and removals of their sequelae of the hand or foot under local anaesthesia with adrenaline-containing lidocaine. Complications were noted in 7 cases, including surgical-site infections in 4 cases, minor bleeding in 2 cases, and wound dehiscence in 1 case.

2.3.1.2 488 hand surgeries with local anesthesia with epinephrine, without a tourniquet, without sedation, and without an anesthesiologist. (Rev Bras Ortop. 2018; 53: 281-6)

The authors investigated the incidence of digital infarction finger vascular occlusion and necrosis in surgeries using local anaesthesia with adrenaline-containing lidocaine in wrists, hands, or fingers. No vascular occlusion nor necrosis was noted in all the cases of local anaesthesia (53 in wrists, 307 in hands, and 128 in fingers).

2.3.1.3 Digital revascularization and replantation using the wide-awake hand surgery technique. (J Hand Surg Eur 2017; 42: 621-5)

The authors reported five digital devascularizations to treat trauma and eight amputations that underwent revascularization and replantation surgery, respectively, using the 'wide-awake' anaesthetic technique. A temporary digital tourniquet (within 5 minutes) was used in 3 cases. Anastomoses were performed without a tourniquet. All cases had successful re-establishment of blood flow with good perfusion to the digital tips. Superficial soft tissue necrosis was noted in 4 cases but that resolved.

2.3.1.4 Digital Necrosis After Lidocaine and Epinephrine Injection in the Flexor Tendon Sheath Without Phentolamine Rescue. (J Hand Surg Am. 2017; 42: e119-23)

The authors reported a case of finger necrosis and subsequent amputation in a patient after adrenaline-containing lidocaine was injected for trigger finger release.

2.3.1.5 Do Not Use Epinephrine in Digital Blocks: Myth or Truth? Part II. A Retrospective Review of 1111 Cases. (Plast Reconstr Surg. 2010; 126: 2031-4)

The authors conducted a review of 1 111 surgery cases involving digital block anaesthesia (using lidocaine in 500, adrenaline-containing lidocaine in 611). Patients with hemorrhagic trauma or peripheral vascular compromise did not receive adrenaline-containing lidocaine. No patients suffered from digital gangrene, nerve injury, or unusually delayed wound healing in the adrenaline-containing lidocaine group.

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2.3.1.6 Local anesthesia using buffered 0.5% lidocaine with 1:200,000 epinephrine for tumors of the digits treated with Mohs micrographic surgery. (J Am Acad Dermatol. 2009; 61: 639-43)

The authors reviewed 63 cases (59 fingers, 4 toes) undergoing Mohs surgeries of the digits under local anaesthesia with adrenaline-containing lidocaine. There were no cases of digital ischemia or necrosis.

2.3.1.7 Dupuytren's Fasciectomy in 60 Consecutive Digits Using Lidocaine with Epinephrine and No Tourniquet. (Plast Reconstr Surg. 2005; 115: 802-10)

The authors conducted a retrospective review comparing 60 digits undergoing fasciectomy for Dupuytren's contracture under local anaesthesia with adrenaline-containing lidocaine without a tourniquet and 43 digits undergoing the same surgery under general anaesthesia, intravenous anaesthesia, or brachial plexus block. Complications including digital nerve and artery injuries, infections, and haematomas were similar between the two groups. There were no cases of digital necrosis in the adrenalin-containing lidocaine group, even though one case sustained a transection of a digital artery at the proximal interphalangeal joint.

2.3.1.8 Digital blocks with adrenaline. An old dogma refuted. (J Hand Surg Br. 1998; 23: 17-9)

Digital blocks with adrenalin-containing lidocaine were performed and digital arterial blood flow was measured in 10 cases. Digital blood flow was temporarily reduced, but perfusion of the digits persisted in every case.

2.3.1.9 Accidental epinephrine auto-injector-induced digital ischemia reversed by phentolamine digital block. (J Am Osteopath Assoc. 1995; 95: 377-8)

The authors reported a case of accidental injection of adrenaline to the right thumb. Discoloration and coldness of the finger due to ischemia were noted.

2.3.1.10 Epinephrine-induced vasospasm reversed by phentolamine digital block. (Am J Emerg Med. 1990; 8: 46-7)

The authors reported a case of accidental injection of adrenaline to a finger. Pain, coldness, and skin pallor were noted in the finger. No tissue necrosis occurred.

2.3.1.11 Post-traumatic Digital Gangrene Associated with Epinephrine Use in Primary Raynaud's Phenomenon: Lesson for the Future. (Ethiop J Health Sci. 2016; 26: 401-4)

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The authors reported a case of the suture of a traumatic laceration following administration of adrenalin-containing lidocaine. Adrenalin-containing lidocaine was administered when suturing traumatic laceration extending from the palmar surface of the fifth digit to the base of the fourth digit. The patient experienced severe pain and discoloration in the sutured site immediately after the operation, and gangrene spread over a 2-hour period to involve the entire fifth digit, which was subsequently amputated. Because of the concern that the gangrene might spread to the fourth digit, the patient was transferred to another hospital for detailed examination, where a diagnosis of primary Raynaud's phenomenon was made. Vasodilatory therapy was performed, and ischemia resolved. The post-operative course over a seven-week period was uneventful.

2.3.1.12 Digital gangrene in a patient with primary Raynaud's phenomenon (J R Coll Physicians Edinb. 2012; 42: 24-6)

A patient with primary Raynaud's phenomenon underwent surgery for paronychia using adrenaline-containing lidocaine and developed digital gangrene.

2.3.1.13 A randomized controlled trial of trigger finger release under digital anesthesia with (WALANT) and without adrenaline. (J Orthop Surg. 2019; 27: Epub 2309499019833002)

A randomized controlled study was conducted to evaluate efficacy and safety of lidocaine (with tourniquet) vs. adrenaline-containing lidocaine in 86 cases scheduled for trigger finger release wide-awake surgery. 74% (32/43) in the adrenaline-containing lidocaine group had good surgical field visibility⁸ compared to 44% (19/43) in the lidocaine group. Duration of anaesthesia was longer in the adrenaline-containing lidocaine group than the lidocaine group with a 2.77-h difference. No skin pallor, necrosis, or post-operative complication was observed in either group.

2.3.1.14 Use of adrenalin with lidocaine in hand surgery (Rev Bras Ortop. 2014; 49: 452-60)

A prospective study was conducted in 41 cases undergoing wrist, hand, and finger surgeries using adrenalin-containing lidocaine. No post-operative necrosis or hematoma was observed in any of the patients.

⁸ Surgeons assessed surgical field visibility score of 10 levels (1: minimum blood loss - 10: large blood loss). Scores 1 - 3, 4 - 6, and 7 - 10 indicate good, moderate, and poor visibility, respectively.

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2.3.2 Excerpt from references cited in the US guidelines⁹

2.3.2.1 Changes in acral blood flux under local application of ropivacaine and lidocaine with and without an adrenaline additive: A double-blind, randomized, placebo-controlled study. (Clin Hemorheol Microcirc. 2008; 38: 279-88)

Laser doppler flowmetry was used to evaluate blood flux at the finger pads of 20 subjects having no cardiovascular disease following Oberst's-method anaesthetic blocks with 6 mL of ropivacaine, lidocaine, adrenaline-containing lidocaine, or saline (20 digits each). Administration of adrenaline-containing lidocaine led to a reduction of 55% in blood flux at 16 minutes after administration compared to before administration, but reduction resolved 40 minutes after administration. No change was observed in perfusion 6 and 24 hours after administration.

2.3.2.2 Epinephrine in Digital Block: Color Doppler Flow Imaging (Dermatol Surg. 2004; 30: 508-11)

In a study in 24 subjects (fingers of 15 subjects and toes of 9 subjects) undergoing surgical procedure¹⁰ under digital blocking with adrenaline-containing lidocaine, digital artery blood flows were measured with color Doppler flow imaging before digital blocking and at 10, 60, and if needed 90 minutes after blocking. There was a statistically significant decrease in blood flow rates after blocking (peak systolic flow velocity [mean ± SD]) decreased from 27.06 ± 5.41 cm/s before blocking to 10.85 ± 6.02 cm/s 10 minutes after blocking, end diastolic flow velocity from 10.83 ± 1.86 cm/s before blocking to 0.95 ± 2.10 cm/s 10 minutes after blocking) ($p < 0.05$, Wilcoxon test), which was restored 60 minutes after blocking in all subjects. At 10 minutes after digital block, 4 in 24 cases had no measurable blood flow, which was restored 60 or 90 minutes after blocking. No systemic or local complication related to adrenaline use was observed.

2.3.2.3 Do Not Use Epinephrine in Digital Blocks: Myth or Truth? Part II. A Retrospective Review of 1111 Cases. (Plast Reconstr Surg. 2010; 126: 2031-4)

Same as in 2.3.1.5

2.3.2.4 Epinephrine-supplemented local anesthetics for ear and nose surgery: Clinical use without complications in more than 10,000 surgical procedures. (J Dtsch Dermatol Ges. 2005; 3: 195-9)

⁹ The references cited in the US guidelines are shown except for literature reviews. Literature reviews were excluded because some of them included cocaine, which shares no structural similarity with lidocaine.

¹⁰ Patients having no peripheral angiopathy, diabetes mellitus, cardiovascular problems, or digital infection, necrosis, or fracture.

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The authors investigated 10 201 cases (about 12% receiving surgery of ears) undergoing surgery involving ears or nose using adrenaline-containing local anaesthetics. Patients with serious coagulation disorder (PT-INR > 1.7) were excluded from the study. No necrosis related to the use of adrenaline was observed in any of the surgery cases.

2.3.2.5 Dupuytren's Fasciectomy in 60 Consecutive Digits Using Lidocaine with Epinephrine and No Tourniquet. (Plast Reconstr Surg. 2005; 115: 802-10)

Same as in 2.3.1.7

2.3.2.6 A Multicenter Prospective Study of 3,110 Consecutive Cases of Elective Epinephrine Use in the Fingers and Hand: The Dalhousie Project Clinical Phase. (J Hand Surg Am. 2005; 30: 1061-7)

A prospective study was conducted in patients who received local anaesthesia with adrenaline in elective surgeries of hands and fingers. Adrenaline was not administered to patients with a major problem potentially causing digital ischaemia (history of digital embolism, serious acute crush injury, history of re-transplantation, Buerger's disease, repair surgery following Dupuytren's contracture surgery, serious angiospasm). No digital necrosis was observed in any of the 3 110 cases who received digital injection of adrenaline.

2.3.2.7 Do Not Use Epinephrine in Digital Blocks: Myth or Truth? (Plast Reconstr Surg. 2001; 107: 393-7)

A double-blind study was conducted to compare adrenaline-containing lidocaine with lidocaine alone for digital block anaesthesia by dorsal approach in surgeries to treat posttraumatic injuries or elective conditions in 60 cases. Patients in the lidocaine alone group (n = 29) experienced flap failure and exacerbated infection after whitlow incision and debridement (n = 1 each), while no patients in the adrenaline-containing lidocaine group (n = 31) experienced such conditions.

2.3.2.8 Subcutaneous Single Injection Digital Block with Epinephrine. (Anesthesiol Res Pract. 2012; doi:10.1155/2012/487650)

Single doses of lidocaine and adrenaline-containing lidocaine were injected for a digital block in the right and left middle fingers, respectively, of 9 healthy adults. The time to anaesthesia of the fingers was shorter and the duration of anaesthesia was longer in the adrenaline-containing lidocaine group compared to the lidocaine alone group. There was no significant difference in the value of SpO₂ between the groups before and at 60 minutes after the digital block, and no ischemic injury or late complications was noted in any of the cases.

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2.4 Standard textbooks used in Japan and other countries

2.4.1 Fitzpatrick's Dermatology, 9th edition (Kang, Sewon, 2019)

It is stated that a small amount of local anaesthetics containing a low dose of adrenaline can be safely used for anaesthesia of terminal body sites, such as digits, tip of nose, and penis, provided that it is used carefully.

2.4.2 Middle Ear and Mastoid Microsurgery, 2nd edition (by Mario Sanna, Hiroshi Sunose, Fernando Mancini, Alessandra Russo, Abdelkader Taibah, Maurizio Falcioni; translated by Hiroshi Sunose, 2013)

It is stated that anaesthetics containing lidocaine and adrenaline should be used for postauricular injection to deliver local anaesthesia in middle ear surgeries. For patients with a cardiac condition in which use of adrenaline is considered a risk, anaesthetics should be prepared without adrenaline. A compound of lidocaine and adrenaline is recommended also for injection into the external auditory canal.

2.4.3 Tympanoplasty, Mastoidectomy, and Stapes Surgery (by Ugo Fisch; translated by Ken Hayashi, 2015)

It is stated that lidocaine and adrenaline should be used for local anaesthesia in tympanoplasty.

3. Description in package inserts of adrenaline products in Japan

In the package inserts of adrenaline injections indicated for prolongation of the action of local anaesthetics and prevention and treatment of intraoperative local haemorrhage as specified in the section "Indications," it is described that they should not be administered to ears, digits, or penis when added to a local anaesthetic in the paragraph "Addition to local anaesthetics" of the section "Precautions Concerning Use."

4. Reports of adverse reactions in Japan

Adverse reaction following an injection to ears or digits in Japan reported to the PMDA from the approval holders of this drug or other adrenaline injections¹¹ by any of the MedDRA preferred terms (PTs) of "necrosis," "injection site necrosis," "injection site injury,"

¹¹ Adrenaline injections that are indicated for prolongation of the action of local anaesthetics and for prevention and treatment of intraoperative local haemorrhage as specified in the Indications section.

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“injection site ischaemia,” or “skin necrosis¹²” has been 1 event of “skin necrosis” in 1 case. The outcome of this case was “resolved.”

(search period: April 1, 2004 to August 10, 2020).

5. Study reports and reports of measures

Of the study reports and reports of measures submitted from the approval holders of this drug and adrenaline injections¹¹ to PMDA, only 1 report about the use of adrenaline in surgery of hypospadias described non-infectious ischaemia and necrosis occurring in the injection site. There was no report involving ears or digits (search period: April 1, 2004 to August 10, 2020).

6. PMDA’s conclusion based on the investigation results

PMDA concludes as follows based on the investigation results about descriptions in package inserts of other countries, relevant guidelines, standard textbooks used in Japan and other countries, published literature, and cases of adverse reactions reported in Japan.

Although a decrease in regional blood flow is pharmacologically anticipated following the injection to ears and digits, the PMDA concluded that injection to ears and digits may be removed from the contraindications for the following reasons:

- Injection of adrenaline-containing anaesthetics to ears and digits is recommended or indicated as an anaesthetic approach in the representative standard textbooks used in Japan and other countries as well as the US guidelines.
- The blood flow in ears is supplied by multiple vessels, making the occurrence of ischaemia following administration of this drug unlikely.
- There is a report that indicates recovery in digital blood flow after a certain period of time without sequela (see 2.3.2.2).

As mentioned above, however, a decrease in local blood flow is pharmacologically anticipated, a small number of adverse reactions have been reported in Japan, and published literature also includes some case reports of digital necrosis. Therefore, a certain level of precaution was considered necessary regarding ears and digits.

Concerning the details of the precaution, the JSSH and JSSF requested that preferably the dose be reduced or injection be discouraged in patients with expected risk of blood flow disorder due to smoking habit, diabetes mellitus, Raynaud’s phenomenon, haemodialysis, digital replantation, or digital crush injury, patients undergoing surgery of multiple adjacent digits, and pediatric patients. Having reviewed the requests, PMDA decided that this drug

¹² The expert advisors supported the appropriateness of the MedDRA PTs used for searching reports of adverse reactions.

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should be used cautiously in these patients because of anticipated blood flow disorder and decreased blood flow, and that a precaution needs to be inserted in the section “Careful Administration.”

The expert advisors presented the following views on the decision by the PMDA and supported the decision.

- Although ischaemia of digits can occur anatomically from the injection site to the areas distal to the injection site, published literature suggests that the extent of ischemia is clinically acceptable.
- The concentration of adrenaline in “Xylocaine Injection 2% with Epinephrine (1:80 000)” used in Japan is slightly higher than that of adrenaline used in products of other countries (1:100 000 or 1:200 000) according to the published overseas literature. However, since not only the concentration but also the total dose used in treatment is relevant, there is no need to exclude this product alone from the lifting of the contraindications.
- Selecting suitable patients is important, and being careful such as by considering the balance between benefits and risks is necessary.

IV. Overall evaluation

Based on the results of the investigations, PMDA considers that the revision of precautions in the package insert as in Appendix 3 is appropriate. (Appendix 3 is not included here. Please refer to the Revision of Precautions of this drug.)

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Appendix 1

Brand name	Indications	Dosage and administration
Xylocaine Injection 0.5% with Epinephrine (1:100,000)	Epidural anaesthesia, conduction anaesthesia, infiltration anaesthesia	<p>Epidural anaesthesia: [Reference maximum dosage: 100 mL/dose] In general, adults use 5 - 30 mL. A dose of 5 - 20 mL is used for sympathetic block.</p> <p>Conduction anaesthesia: [Reference maximum dosage: 100 mL/dose] In general, adults use 3 - 40 mL. A dose of up to 5 mL is used for intercostal block.</p> <p>Infiltration anaesthesia: [Reference maximum dosage: 100 mL/dose] In general, adults use 2 - 40 mL.</p> <p>In all the anaesthetic approaches, the dosage should be adjusted according to the age, regions to be anaesthetized, sites, tissue, symptoms, or body constitution as appropriate.</p>
Xylocaine Injection 1% with Epinephrine (1:100,000)	Epidural anaesthesia, conduction anaesthesia, infiltration anaesthesia, surface anaesthesia	<p>Epidural anaesthesia: [Reference maximum dosage: 50 mL/dose] In general, adults use 10 - 30 mL.</p> <p>Conduction anaesthesia: [Reference maximum dosage: 50 mL/dose] In general, adults use 3 - 20 mL. A dose of up to 5 mL is used for intercostal block.</p> <p>Infiltration anaesthesia: [Reference maximum dosage: 50 mL/dose] In general, adults use 2 - 40 mL.</p> <p>Surface anaesthesia: An appropriate dose is applied or sprayed.</p>

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		In all the anaesthetic approaches, the dosage should be adjusted according to the age, regions to be anaesthetized, sites, tissue, symptoms, or body constitution as appropriate.
Xylocaine Injection 2% with Epinephrine (1:80 000)	Epidural anaesthesia, conduction anaesthesia, infiltration anaesthesia, surface anaesthesia	<p>Epidural anaesthesia: [Reference maximum dosage: 25 mL/dose] In general, adults use 10 - 20 mL.</p> <p>Conduction anaesthesia: [Reference maximum dosage: 25 mL/dose] In general, adults use 2 - 20 mL.</p> <p>Infiltration anaesthesia: [Reference maximum dosage: 25 mL/dose] In general, adults use 2 - 25 mL.</p> <p>A dose of 0.5 - 2 mL is used for ophthalmologic anaesthesia.</p> <p>Surface anaesthesia: An appropriate dose is applied or sprayed.</p> <p>In all the anaesthetic approaches, the dosage should be adjusted according to the age, regions to be anaesthetized, sites, tissue, symptoms, or body constitution as appropriate.</p>

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Appendix 2

Description in the overseas package inserts

<p>The US (November 2018)</p>	<p>Xylocaine (lidocaine HCl Injection, USP) Xylocaine (lidocaine HCl and epinephrine Injection, USP)</p>	<p><u>PRECAUTIONS:</u> Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully circumscribed quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.</p>
<p>The UK (June 2018)</p>	<p>Xylocaine 1% with Adrenaline Xylocaine 2% with Adrenaline</p>	<p><u>Contraindications</u> The use of a vasoconstrictor is contraindicated for anaesthesia of fingers, toes, tip of nose, ears and penis.</p>
<p>Canada (June 2018)</p>	<p>1% lidocaine hydrochloride (10 mg/mL) with 1:200,000 epinephrine (0.005 mg/mL) 1% lidocaine hydrochloride (10 mg/mL) with 1:100,000 epinephrine (0.010 mg/mL) 2% lidocaine hydrochloride (20 mg/mL) with 1:200,000 epinephrine (0.005 mg/mL)</p>	<p><u>WARNINGS AND PRECAUTIONS</u> Use of Parenteral Solutions Containing Epinephrine: XYLOCAINE Parenteral Solutions containing epinephrine should not be used in areas of the body supplied by end arteries, such as digits, nose, ears or penis, or otherwise having a compromised blood supply (see also DRUG INTERACTIONS).</p>

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Australia (June 2017)	XYLOCAINE AND XYLOCAINE WITH ADRENALINE	<u>CONTRAINDICATIONS</u> Solutions with adrenaline must not be used for local analgesia in parts of the body with compromised blood supply or supplied by end arteries, such as fingers, toes, nose, ears or penis. There is a possibility of producing arterial vasoconstriction and subsequent ischaemic gangrene distal to the site of injection.
Germany (February 2015)	Xylocitin 2 % mit Epinephrin (Adrenalin) 0,001 % (1:100 000) Injektionslösung	<u>Gegenanzeigen</u> Wegen der gefäßverengenden Wirkung des Epinephrin-Anteils darf Xylocitin 2 % mit Epinephrin (Adrenalin) 0,001 % (1:100 000) weiterhin nicht angewendet werden bei - Betäubungen in Endstromgebieten der Blutgefäße ¹³
France (March 2019)	XYLOCAINE 10 mg/ml ADRENALINE 0,005 mg/ml, solution injectable	<u>Contre-indications</u> Les formes adrénalinées ont de plus comme contre-indications : · Anesthésie par infiltration locale au niveau des extrémités (doigt, verge). ¹⁴

¹³ Approximate translation by the PMDA: The product, which contains vasoconstrictive epinephrine, should not be used. - Anaesthesia of the terminal parts of blood vessels

¹⁴ Approximate translation by the PMDA: The adrenaline product has another contraindication: Local infiltration anaesthesia of terminal parts (fingers, penis)