超音波吸引器の使用上の注意の改訂について

1. これまでの経緯

平成26年4月に米国食品医薬品局（FDA）から、モルセレータ※1の使用に際しては、「子宮筋腫がある女性の腹腔鏡下の子宮摘出術や子宮筋腫核出術にモルセレータを使用した細切除術を実施した場合、想定されていなかったがん組織、特に子宮肉腫を腹腔内に播種させるリスクがある。」と報告された（資料1）。これを受け、厚生労働省、独立行政法人 医薬品医療機器総合機構及び関係学会で検討を行い、モルセレータを悪性腫瘍又はその疑いがある場合に使用することを禁止するため、平成28年7月に、厚生労働省医薬・生活衛生局医療機器審査管理課及び安全対策課より、使用上の注意の改訂に係る事務連絡（資料2）が発出された。

平成29年10月30日にFDAは、超音波吸引器について、子宮筋腫に使用すべきではないとする旨のガイダンスを発出した。（資料3）

※1 モルセレータとは、内視鏡使用下において体腔内に挿入し、組織を切除するために用いる内視鏡用能動切除器具。

2. 超音波吸引器に係るFDAのガイダンスについて

超音波吸引器に係るFDAが発出したガイダンスの概要は以下の通り。

- 超音波吸引器とは、機械的超音波振動によって組織を断片化/乳化し、吸引することを目的とする外科用ツールである。
- 超音波吸引器は、神経外科手術、整形外科手術、一般手術、婦人科手術等の広範囲な外科手術に使用することができる。
- 超音波吸引器は、デバルキング※2目的で使用されることがある。
- 超音波吸引器を悪性腫瘍の断片化/乳化に使用すると、播種の可能性がある。
- 超音波吸引器が子宮筋腫の除去のために使用されている状況をFDAは認識していないものの、術前に子宮筋腫と子宮肉腫を明確に区別する方法が確立していないため、子宮筋腫がある患者に使用した場合、想定されていなかった子宮肉腫を播種させる可能性がある。
- 超音波吸引器を子宮筋腫がある患者に使用することによる想定されていなかった子宮肉腫の播種のリスクは、代替治療が存在する状況にあっては、患

者にとっていかなるベネフィットをも上回るものである。

※2 デバルキングとは、腫瘍の一部を切除することであり、残った腫瘍は二期的切除術や、化学療法、放射線治療等により治療される。

3. 日本における措置の検討

平成 29 年 10 月 30 日の FDA のガイダンスを受け、日本における超音波吸引器に対する措置の要否について以下のとおり検討した結果、子宮筋腫がある患者に使用した場合の想定されていなかった子宮肉腫の播種のリスクを考慮し、使用上の注意の改訂が必要であるとの結論に至った。

1)対象となる製品について

超音波を使用する医療機器は多数存在するが、一般的に手術に使用される医療機器は、高周波帯域の波長でジュール熱作用やスパーク等を起こし、組織の切開/凝固を行うものと、低周波帯域の波長で振動を起こし、組織内部にエネルギーを吸収させ、破砕/乳化を行うものがある。破砕/乳化は、出血や組織変性が少ないことが特徴であり、播種のおそれは、超音波による腫瘍組織の破砕/乳化の際に発生することから、今回の措置の対象となる製品は、吸引機能の有無にかかわらず、超音波により組織を「破砕」又は「乳化」する機能を有する医療機器であると考える。

なお、現状において上記に該当することが分かっている医療機器を、資料4に示す。

2)使用状況をふまえた措置の検討

現状、本邦では、子宮筋腫がある患者に対して、MRI 検査、細胞診、血清 LDH 測定などの術前検査により悪性疾患の除外診断が行われているものの、摘出前に確定診断を下すことは不可能であり、術後に初めて悪性と判明する場合がある。本件と同様の事例としては、子宮筋腫がある患者に対して、腹腔鏡下の子宮摘出術や子宮筋腫核出術を実施する際にモルセレータを使用して組織を細切する場合について、悪性腫瘍が疑われる患者に対しては使用しないよう、平成 28 年 7 月に、使用上の注意の改訂に係る事務連絡が発出されたところである。また臨床現場においても、腫瘍細胞が転移する危険性を考慮し、術前の MRI 診断と病理学的診断等により悪性の可能性を除外すること、手術実施に際し、徹底した術前評価にも関わらず診断不可能な悪性病変のリスク及び予後を悪化させるリスクに対して十分にインフォームドコンセントを得ること等の留意点が、一般社団法人 日本産科婦人科内視鏡学会発行の会告「腹腔鏡の子宮摘出術と子宮筋腫核出術の電動モルセレータの使用について」(日本産科婦人科内視鏡学会雑誌 Vol.30No.1. 2014)や、公益社団法人 日本産婦人科医会発行の「研修ノート No.96 子宮筋腫」に記載されて

いる。

一方、子宮筋腫に対して超音波吸引器を使用する治療方法は、関連学会の診療ガイドライン等に記載されておらず、専門家の意見によれば標準的な手技とは言えないこと、そのため臨床現場における子宮筋腫に対する超音波吸引器の使用実態がほとんど想定されないことに鑑みると、超音波吸引器以外の代替治療の選択が可能な状況も踏まえ、悪性変化の否定できない子宮筋腫に対して超音波吸引器を使用することは許容できないと考える。

3)添付文書改訂案

添付文書の【禁忌・禁止】の項に、以下の内容を記載すること。

悪性変化の否定できない子宮筋腫の乳化又は破砕には使用しないこと[組織片が飛散することで、腫瘍細胞が転移するおそれがある。]

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Laparoscopic Uterine Power Morcellation in Hysterectomy and Myomectomy: FDA Safety Communication

FDA issued an **updated safety communication (/MedicalDevices/Safety/AlertsandNotices/ucm424443.htm)** on November 24, 2014

Date Issued: April 17, 2014

Audience:

- Health Care Providers
- Medical Professional Associations
- Cancer Advocacy Organizations
- Health Care Facilities/Hospitals
- Women with Symptomatic Uterine Fibroids who are Considering Surgical Options
- Manufacturers of Devices used for Minimally Invasive Surgeries

Medical Specialties: Pathology, Internal Medicine, Nursing, Obstetrics/Gynecology, Oncology

Product:
Laparoscopic power morcellators are medical devices used during different types of laparoscopic (minimally invasive) surgeries. These can include certain procedures to treat uterine fibroids, such as removing the uterus (hysterectomy) or removing the uterine fibroids (myomectomy). Morcellation refers to the division of tissue into smaller pieces or fragments and is often used during laparoscopic surgeries to facilitate the removal of tissue through small incision sites.

Purpose:
When used for hysterectomy or myomectomy in women with uterine fibroids, laparoscopic power morcellation poses a risk of spreading unsuspected cancerous tissue, notably uterine sarcomas, beyond the uterus. Health care providers and patients should carefully consider available alternative treatment options for symptomatic uterine fibroids. Based on currently available information, the FDA discourages the use of laparoscopic power morcellation during hysterectomy or myomectomy for uterine fibroids.

Summary of Problem and Scope:
Uterine fibroids are noncancerous growths that develop from the muscular tissue of the uterus. Most women will develop uterine fibroids (also called leiomyomas) at some point in their lives, although most cause no symptoms[1]. In some cases, however, fibroids can cause symptoms, including heavy or prolonged menstrual bleeding, pelvic pressure or pain, and/or frequent urination, requiring medical or surgical therapy.

Many women choose to undergo laparoscopic hysterectomy or myomectomy because these procedures are associated with benefits such as a shorter post-operative recovery time and a reduced risk of infection compared to abdominal hysterectomy and myomectomy[2]. Many of these laparoscopic procedures are performed using a power morcellator.

A number of additional treatment options are available for women with symptomatic uterine fibroids including traditional surgical hysterectomy (performed either vaginally or abdominally) and myomectomy, laparoscopic hysterectomy and myomectomy without morcellation, laparotomy using a smaller incision (minilaparotomy), deliberate blocking of the uterine artery (catheter-based uterine artery embolization), high-intensity focused ultrasound, and drug therapy. Evidence demonstrates that, when feasible, vaginal hysterectomy is associated with comparable or better results and fewer complications than laparoscopic or abdominal hysterectomy[3].

Importantly, based on an FDA analysis of currently available data, it is estimated that 1 in 350 women undergoing hysterectomy or myomectomy for the treatment of fibroids is found to have an unsuspected uterine sarcoma, a type of uterine cancer that includes leiomyosarcoma. **If laparoscopic power morcellation is performed in women with unsuspected uterine sarcoma, there is a risk that the procedure will spread the cancerous tissue within the abdomen and pelvis, significantly worsening the patient's likelihood of long-term survival. For this reason, and because there is no reliable method for predicting whether a woman with fibroids may have a uterine sarcoma, the FDA discourages the use of laparoscopic power morcellation during hysterectomy or myomectomy for uterine fibroids.**

Recommendations for Health Care Providers:

- Be aware that based on currently available information, the FDA discourages the use of laparoscopic power morcellation during hysterectomy or myomectomy for the treatment of women with uterine fibroids.
- Do not use laparoscopic uterine power morcellation in women with suspected or known uterine cancer.
- Carefully consider all the available treatment options for women with symptomatic uterine fibroids.
- Thoroughly discuss the benefits and risks of all treatments with patients.
- For individual patients for whom, after a careful benefit-risk evaluation, laparoscopic power morcellation is considered the best therapeutic option:
    - Inform patients that their fibroid(s) may contain unexpected cancerous tissue and that laparoscopic power morcellation may spread the cancer, significantly worsening their prognosis.
    - Be aware that some clinicians and medical institutions now advocate using a specimen "bag" during morcellation in an attempt to contain the uterine tissue and minimize the risk of spread in the abdomen and pelvis.

Recommendations for Women:

- Ask your health care provider to discuss all the options available to treat your condition and discuss the risks and benefits of each.

- If laparoscopic hysterectomy or myomectomy is recommended, ask your health care provider if power morcellation will be performed during your procedure, and to explain why he or she believes it is the best treatment option for you.
- If you have already undergone a hysterectomy or myomectomy for fibroids, tissue removed during the procedure is typically tested for the presence of cancer. If you were informed these tests were normal and you have no symptoms, routine follow-up with your physician is recommended. Patients with persistent or recurrent symptoms or questions should consult their health care provider.

FDA Actions:
The FDA is concerned about women undergoing laparoscopic power morcellation for the treatment of uterine fibroids and the risk of inadvertent spread of unsuspected cancer to the abdominal and pelvic cavities. In an effort to enhance understanding of the problem and provide information on the appropriate use of laparoscopic power morcellators, the FDA:

- Instructed manufacturers of power morcellators used during laparoscopic hysterectomy and myomectomy to review their current product labeling for accurate risk information for patients and providers;
- Will convene a public meeting of the Obstetrics and Gynecological Medical Device Advisory Committee to discuss: 1) the clinical role of laparoscopic power morcellation in the treatment of uterine fibroids, 2) whether surgical techniques and/or use of accessories, such as morcellation/specimen bags, can enhance the safe and effective use of these devices, and 3) whether a “boxed warning” related to the risk of cancer spread should be required for laparoscopic power morcellators;
- Will continue to review adverse event reports, peer-reviewed scientific literature, and information from patients, health care providers, gynecologic and surgical professional societies, and medical device manufacturers.

Reporting Problems to the FDA:
Prompt reporting of adverse events can help the FDA identify and better understand the risks associated with medical devices. If you suspect that a morcellator and/or specimen bag has malfunctioned or contributed to a serious injury or adverse outcome, the FDA encourages you to file a voluntary report through **MedWatch, the FDA Safety Information and Adverse Event Reporting program (/Safety/MedWatch/HowToReport/ucm2007306.htm)**.

Health care professionals employed by facilities that are subject to the **FDA's user facility reporting requirements (/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm2005737.htm)** should follow the reporting procedures established by their facilities.

Other Resources:

- **Society of Gynecologic Oncology (SGO)’s position statement on morcellation published in December 2013 (https://www.sgo.org/newsroom/position-statements-2/morcellation/)**
- **American College of Obstetricians and Gynecologists (ACOG)’s Statement on Choosing the Route of Hysterectomy for Benign Disease November 2009 (Reaffirmed 2011) (https://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Gynecologic_Practice/Choosing_the_Route_of_Hysterectomy_for_Benign_Disease)**
- **American Association of Gynecologic Laparoscopists (AAGL)’s AAGL Member Update: Disseminated Leiomyosarcoma With Power Morcellation 2014 (http://www.aagl.org/aaglnews/aagl-member-update-disseminated-leiomyosarcoma-with-power-morcellation/) (http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm)**

References:

[1] NIH Fact Sheet on Uterine Fibroids. March 2013. Available at **http://report.nih.gov/nihfact-sheets/viewfactsheet.aspx?csid=50 (http://report.nih.gov/nihfactsheets/viewfact-sheet.aspx?csid=50)**

[2] Nieboer TE, Johnson N, Lethaby A, et al. Surgical approach to hysterectomy for benign gynecological disease. Cochrane Database Syst Rev. 2009;(3):CD003677.

[3] Ibid.

Contact Information:

If you have questions about this communication, please contact the Center for Devices and Radiological Health's Division of Industry and Consumer Education (DICE) at **DICE@FDA.HHS.GOV (mailto:DICE@FDA.HHS.GOV)**, 800-638-2041 or 301-796-7100.

Additional Information

- **Quantitative Assessment of the Prevalence of Unsuspected Uterine Sarcoma in Women Undergoing Treatment of Uterine Fibroids - Summary and Key Findings (PDF - 253KB) (/downloads/MedicalDevices/Safety/AlertsandNotices/UCM393589.pdf)**

More in Safety Communications (/MedicalDevices/Safety/AlertsandNotices/default.htm)

Information About Heparin (/MedicalDevices/Safety/AlertsandNotices/ucm135345.htm)

Preventing Tubing and Luer Misconnections (/MedicalDevices/Safety/AlertsandNotices/TubingandLuerMisconnections/default.htm)

資料２

事　　務　　連　　絡
平成 28 年 7 月 25 日

（別記１）　御中

厚生労働省医薬・生活衛生局医療機器審査管理課

厚生労働省医薬・生活衛生局安全対策課

モルセレータに係る「使用上の注意」について

モルセレータ（内視鏡使用下において体腔内に挿入し、組織を切除するために用いる内視鏡用能動切除器具）の使用にあたっては、「子宮筋腫がある女性の腹腔鏡下の子宮摘出術や子宮筋腫核出術にモルセレータを使用した細切除術を実施した場合、想定されていなかったがん組織、特に子宮肉腫を腹腔内に播種させるリスクがある。」ことが米国食品医薬品局（ＦＤＡ）より報告されているところです。

これを受け、厚生労働省、独立行政法人　医薬品医療機器総合機構及び関係学会で検討を行った結果、今後、新たに承認又は認証されるモルセレータの添付文書における「使用上の注意」の記載方法について、下記のように取扱うこととしましたので、今後の市販後の適正使用確保のために御了知ください。

なお、同旨の事務連絡を医薬品医療機器等法登録認証機関協議会及び独立行政法人　医薬品医療機器総合機構宛てに送付していることを申し添えます。

記

1. モルセレータについては、添付文書の【禁忌・禁止】の項に以下の内容を記載すること。

   悪性腫瘍又はその疑いがある場合は使用しないこと。［組織片が飛散することで、腫瘍細胞が転移する危険性がある。］

2. モルセレータについては、添付文書の【使用上の注意】の［重要な基本的注意］の項に以下の内容を記載すること。

   本製品の使用に際しては、診断不可能な悪性病変の可能性及び予後を悪化させる可能性について、患者に十分な情報提供を行い、同意を得た上で使用すること。

（別記１）

一般社団法人 日本医療機器産業連合会

一般社団法人 米国医療機器・IVD 工業会

欧州ビジネス協会医療機器委員会

資料 3

Contains Nonbinding Recommendations

Product Labeling for Certain Ultrasonic Surgical Aspirator Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 30, 2017.

The draft of this document was issued on November 10, 2016.

For questions about this document, contact the Obstetrics-Gynecology Devices Branch, 301-796-7030 for gynecologic indications, or the General Surgery Devices Branch 2, 301-796-6970 for general surgical indications.

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2016-D-3275. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1500072 to identify the guidance you are requesting.

Product Labeling for Certain Ultrasonic Surgical Aspirator Devices

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The Food and Drug Administration (FDA) is issuing this guidance to recommend the addition of a specific safety statement to the product labeling of certain ultrasonic surgical aspirator devices. Ultrasonic surgical aspirator devices are surgical tools intended to fragment, emulsify and aspirate hard and soft tissue. These devices can be used in many different surgical specialties for a wide range of procedures, including the debulking of malignant tumors. Ultrasonic surgical aspirators cause tissue fragmentation through the delivery of ultrasound energy to target tissue through an oscillating tip. Tissue fragments are aspirated through the inner lumen of the device. This mechanism of action creates the potential for tissue dissemination. The incorporation of suction/aspiration reduces but cannot eliminate this potential.

In light of the risk of tissue dissemination from use of these devices, the FDA is providing a specific labeling recommendation in this guidance to promote the safe and effective use of ultrasonic surgical aspirator devices.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

Ultrasonic surgical aspirator devices may be indicated for use in a wide range of surgical applications, including but not limited to neurosurgery, plastic and reconstructive surgery, orthopedic surgery, laparoscopic surgery, open surgery, and gynecologic surgery. Because ultrasonic surgical aspirator devices use an oscillating tip to cause tissue fragmentation through

the delivery of ultrasound energy to target tissue, there is the potential for tissue dissemination that is mitigated but not completely eliminated by the use of suction/aspiration.

FDA is aware that ultrasonic surgical aspirator devices are sometimes used to treat advanced malignancy through cytoreduction (also known as debulking). In these cases, the device is used to remove a portion of a malignant tumor that cannot be completely excised, in an effort to enhance the effectiveness of ancillary treatments (such as radiation or chemotherapy). When used in advanced cancers, the risk of adverse clinical effects from tissue dissemination may be small compared to the device's potential benefits, such as more extensive tumor debulking, no/minimal collateral thermal damage, and the ability to avoid resection/removal of organs.

However, in certain clinical circumstances, the unintended dissemination of cancerous cells may have a significant adverse effect that outweighs any demonstrated benefits. FDA is aware that labeling of certain ultrasonic surgical aspirator devices allows for use in the removal of uterine fibroids, although this use may not be explicitly stated in the labeling and FDA is not aware of these devices being used for this purpose.[1] There are currently no reliable preoperative screening procedures to detect uterine sarcoma in women with presumed benign fibroids. Use of an ultrasonic surgical aspirator during treatment for symptomatic uterine fibroids on a woman with an occult uterine sarcoma could result in dissemination of this cancer. This risk of cancer dissemination outweighs any potential benefits in this patient population, particularly since there are alternative treatment options available.

For these reasons, FDA recommends that the labeling of certain ultrasonic surgical aspirator devices include a contraindication against use of the devices for removal of uterine fibroids.

III. Scope

Ultrasonic surgical aspirator devices may have general indications for use (e.g., laparoscopic surgery, open surgery) or specific indications for use (e.g., gynecologic surgery). This guidance, and the labeling recommendation below, applies to ultrasonic surgical aspirator devices with indications for use in laparoscopic surgery, open surgery, or gynecologic surgery as such surgeries can include gynecologic procedures. These devices are regulated under several different product codes, including LFL (Instrument, Ultrasonic Surgical) and NLQ (Scalpel, Ultrasonic, Reprocessed). Some devices regulated under these product codes may utilize different technology (e.g., they do not aspirate), and would not fall within the scope of this guidance.

[1] On November 25, 2014, FDA issued the "Immediately in Effect Guidance Document: Product Labeling for Laparoscopic Power Morcellators" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM424123.pdf) to address new scientific information that represents a significant change to the benefit/risk profile for laparoscopic power morcellators (LPM). Specifically, FDA reviewed scientific information that suggests that the use of LPMs contributes to the dissemination and upstaging of an occult uterine malignancy in women undergoing laparoscopic gynecologic surgery for presumed fibroids. FDA is generally not aware of reports of dissemination or upstaging of occult uterine malignancies related to ultrasonic surgical aspirators at this time. FDA is recommending the contraindication in this guidance, rather than the contraindication in the LPM guidance, in light of the fact that ultrasonic surgical aspirators are generally not intended nor used for the removal of uterine fibroids.

This guidance does not apply to ultrasonic surgical aspirator devices with an indication for use only for other surgical subspecialties, e.g., gastrointestinal and affiliated organ surgery, urological surgery, neurosurgery. For example, this guidance would not apply to devices indicated only for neurosurgical fragmentation and aspiration.

IV. Recommended Labeling Statement

FDA recommends that manufacturers of ultrasonic surgical aspirator devices with indications for use in laparoscopic surgery, open surgery, or gynecologic surgery prominently include the following Contraindication in their product labeling:

> ***CONTRAINDICATION: This ultrasonic surgical aspirator device is not indicated for and should not be used for the fragmentation, emulsification, and aspiration of uterine fibroids.***

In addition to including the above Contraindication in the product labeling, we recommend manufacturers review and update other portions of their labeling to be consistent with this Contraindication. For example, a manufacturer may revise the list of procedures in the labeling for which the ultrasonic surgical aspirator can be utilized.

FDA believes accurate product labeling is important to make health care providers and patients aware of situations when these devices should not be used. FDA believes that the Contraindication is important for the safe and effective use of these ultrasonic surgical aspirator devices.

Within 120 days of the publication of this guidance, a manufacturer with an existing 510(k) clearance should: 1) add the Contraindication to its labeling; 2) submit both the current labeling and revised labeling to the Center for Devices and Radiological Health (CDRH); and 3) provide updated labeling to purchasers of these ultrasonic surgical aspirator devices that have already been distributed.[2]

If a manufacturer with an existing 510(k) clearance adds the Contraindication listed above, FDA does not intend to object if such labeling changes are submitted as an amendment ("add to file") to the existing 510(k) rather than as a new 510(k). We recommend that manufacturers bundle 510(k) amendments for these labeling changes as appropriate.

In addition, manufacturers submitting a new 510(k) for a new or significantly modified device should include these labeling recommendations in the submission.

[2] FDA recommends that a manufacturer provide updated labeling in a way to help ensure purchasers are aware of it, such as posting the updated labeling on the manufacturer's website and notifying purchasers that they can access the updated labeling on that website.

資料４

一般的名称	製造販売業者	製品名	承認・認証番号等
超音波吸引器	アムコ	超音波手術器　CUSA　Excel	21100BZY00633000
超音波手術器	日立製作所	ソノップ　5000	21300BZZ00029000
超音波手術器	オリンパスメディカルシステムズ	超音波手術システム　SonoSurg	21400BZZ00559000
超音波手術器	日本ストライカー	ソノペットUST-2001アルファ	22500BZX00508000
超音波吸引器	EPJメディカルサービス	超音波手術器　CUSA Clarity	23000BZX00065000