PMDA
Medical Safety Information
Pharmaceuticals and Medical Devices Agency

No. 65 March 2023

Precautions for Handling of Sustained-Release preparations

1 Properties of sustained-release preparations and risks when crushed

(Case 1) A prescribing physician prescribed NIFEDIPINE CR for a patient with nasogastric tubes. A nurse was unaware that NIFEDIPINE CR Tablets is a sustained-release preparation. He/she crushed the drug and administered it via a nasogastric tube.

(Case 2) A prescribing physician was not aware that Intuniv Tablets is a sustained-release preparation and instructed that "the tablets should be split to adjust the dose according to the symptoms."

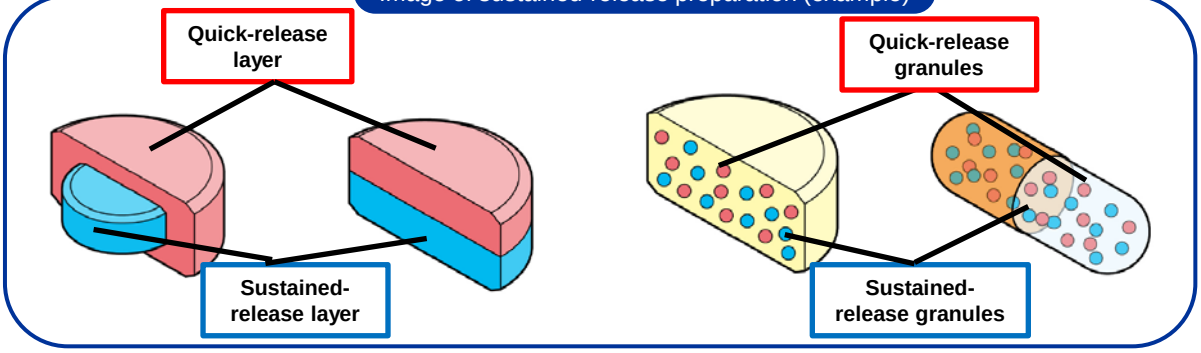
POINT Points to be noted for safe use

- **A sustained-release preparation is a drug product developed to reduce the number of doses, maintain the efficacy, and reduce adverse drug reactions by adjusting the release rate, etc. of the active ingredient.**
- **There have been repeated reports of cases in which sustained-release preparations, whose pharmaceutical characteristics cannot be inferred from their brand/generic names, are crushed/split for administration.**

If you crush or split a sustained-release preparation for administration or if a patient chews a sustained-release preparation when taking the drug, there is a risk of a sudden increase in the blood concentration, which may lead to serious adverse drug reactions, and the expected efficacy cannot be obtained.

- Sudden drop in blood pressure
- Respiratory depression
- Decreased level of consciousness

Image of sustained-release preparation (example)



There have been many reports of cases in which sustained-release preparations, whose pharmaceutical characteristics cannot be inferred from their brand/generic names, are administered after crushing/splitting preparations, even though the drugs should not be split.
See the list on the next page for drugs for which a particularly large number of cases have been reported (e.g., crushing).
Be sure to check a package insert and materials, etc. prepared by each company to see whether the drug can be crushed and split, and consult a pharmacist.

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List of sustained-release preparations for which a particularly large number of reports of administering crushed tablets, etc. have been reported (in the order of Japanese syllabary)

Brand/generic name, etc.	Non-proprietary name	Therapeutic category
Adalat CR tablets **(Generic) NIFEDIPINE CR** **NIFEDIPINE L Tablets**	Nifedipine	Long-acting Ca antagonists, therapeutic agents for hypertension/angina pectoris
Invega Tablets	Paliperidone	Antipsychotic drugs
Intuniv Tablets	Guanfacine hydrochloride	Therapeutic agents for attention deficit/hyperactivity disorder (Selective α2A-adrenoceptor agonists)
EBRANTIL Capsules	Urapidil	Dysuria improving agents/antihypertensive drugs
Graceptor Capsules	Tacrolimus hydrate	Immunosuppressants
Careload LA Tablets	Beraprost sodium	Oral prostacyclin (PGI2) derivatives sustained-release preparations
Concerta Tablets	Methylphenidate hydrochloride	Central nervous system stimulants
THEODUR Tablets **UNIPHYL LA Tablets, UNICON**	Theophylline	Xanthine bronchodilators
Depakene R Tablets, SELENICA-R Tablets **(Generic) SODIUM VALPROATE SR**	Sodium valproate	Antiepileptic drugs, drugs for mania/manic state, drugs for migraine
Toviaz Tablets	Fesoterodine fumarate	Therapeutic agents for overactive bladder
NARUSUS TABLETS * Narcotics	Hydromorphone hydrochloride	Drugs for persistent cancer pain
Fero-Gradumet Tablets	Dried ferrous sulfate	Sustained-release iron preparations
PROTERNOL S Tablets	*dl*-Isoprenaline hydrochloride	Cardiac function/tissue circulation accelerators
Betanis Tablets	Mirabegron	Selective β3 adrenergic receptor agonists for treatment of overactive bladder
ReQuip CR Tablets	Ropinirole hydrochloride	Dopamine D2-receptor agonist
Regnite Tablets	Gabapentin enacarbil	Drugs for restless legs syndrome
Onetram Tablets	Tramadol hydrochloride	Drugs for persistent cancer pain/chronic pain

* The above information is as of March 2023.

Some of the proprietary names of sustained-release preparations may have abbreviations, etc. indicating pharmaceutical characteristics.

(Example)

- **NIFEDIPINE CR Tablets: Controlled Release**
- **SODIUM VALPROATE SR: Sustained Release**
- **Careload LA Tablets: Long Acting**
- **PROTERNOL S Tablets: Slow**

The details of cases including the above drugs can be searched for using the following website. (Only in Japanese)

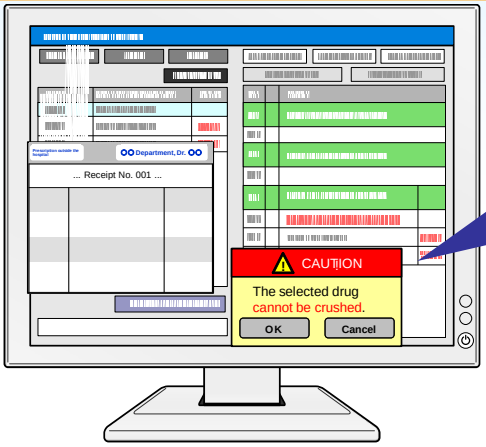
Japan Council for Quality Health Care

Case search in the Project to Collect and Analyze Pharmaceutical Near-miss Events

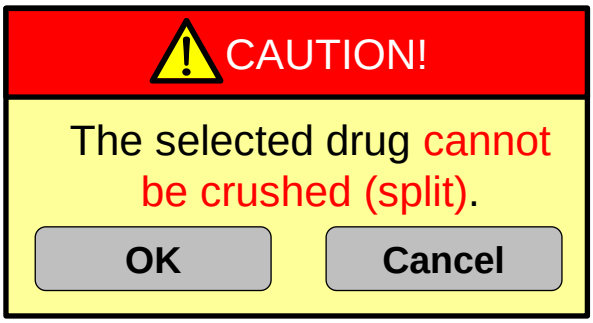
https://www.yakkyoku-hiyari.jcqhc.or.jp/phsearch/SearchReport.action

2 Prevention of administering crushed tablets using a prescription ordering system

For drugs such as sustained-release preparations, add settings so that warnings will be indicated when there are instructions for crushing, etc.



Example of caution statement



Other than the above, the following settings may be added.

- **For sustained-release preparations, a prescription of preparations with unavailable specifications or a prescription with fractional dosages (halving tablets, etc.) is not allowed.**
- **Warnings and comments, etc. are displayed individually according to the characteristics of drugs, such as those that cannot be administered through a tube.**

**The prescription ordering system can be used to prevent administering crushed tablets, etc.
Please consider these measures.**

Notices related to this medical safety information from related organizations are posted on the website of the Pharmaceuticals and Medical Devices Agency (https://www.pmda.go.jp/safety/info-services/medical-safety-info/0178.html) (only in Japanese)

- "Onetram Tablets 100 mg are sustained-release preparations. They should not be split, crushed, or chewed."
- "Adalat CR tablets 10 mg, 20 mg, 40 mg are sustained-release preparations. They should not be split, crushed, or chewed."
- "Betanis Tablets are sustained-release preparations. They should not be split, crushed, or chewed."

* This is information as of March 2023.

Healthcare professionals are requested to be careful not to administer sustained-release preparations using an incorrect method, such as crushing or splitting, and to thoroughly instruct patients so that they will not take the drugs using an incorrect method, such as chewing or splitting tablets.

3 Sustained-release preparations requiring attention to dosage and administration, etc.

(Case 3) A prescribing physician believed that Depakene R Tablets and SELENICA-R Tablets had the same dose regimen because they had the same active ingredients and prescribed SELENICA-R Tablets in a twice-daily regimen. The dosage was changed to once daily as a result of a prescription question.

POINT Points to be noted for safe use

- **Note that there are sustained-release preparations with different dosages and administrations depending on the characteristics of drugs, even if the non-proprietary names are the same.**

Non-proprietary name	Brand/generic name	Remarks
Theophylline	THEODUR Tablets	12 to 24-hour duration
	UNIPHYL LA Tablets, UNICON	24-hour duration
Nifedipine	NIFEDIPINE L Tablets	12-hour duration
	NIFEDIPINE CR Tablets	24-hour duration
	Adalat CR tablets	24-hour duration
Sodium Valproate	SODIUM VALPROATE SR	Oral administration in 1 to 2 divided doses a day
	Depakene R Tablets	Oral administration in 1 to 2 divided doses a day
	SELENICA-R Tablets	Once-daily oral administration

For the drugs shown above, a particularly large number of cases have been reported.

Because the situation differs depending on drugs adopted at your institution, please use the following memo column as appropriate when providing information within the institution.

[Memo column]

About this information

* PMDA Medical Safety Information is issued by the Pharmaceuticals and Medical Devices Agency for the purpose of providing healthcare providers with clearer information from the perspective of promoting the safe use of pharmaceuticals and medical devices. The information presented here has been compiled, with the assistance of expert advice, from cases collected as Medical Accident Information Reports by the Japan Council for Quality Health Care, and collected as Adverse Drug Reaction and Malfunction Reports in accordance with the Law on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices.
* We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future.
* This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibility on them, but is provided as a support to promote the safe use of pharmaceuticals and medical devices by healthcare professionals.
* This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Access to the most up-to-date safety information is provided via the PMDA Medi-navi service.

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