Maklumat tambahan indikasi

Tahun 2021

Products Approved For Additional Indication (DCA 363 – 9 September 2021)

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
1.	VENCLEXTA TABLET 10MG [Venetoclax 10mg] VENCLEXTA TABLET 50MG [Venetoclax 50mg] VENCLEXTA TABLET 100MG [Venetoclax 100mg]	**INDICATION :** VENCLEXTA is indicated, in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukaemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. **POSOLOGY:** Acute Myeloid Leukaemia The recommended dosage and ramp-up of VENCLEXTA depends upon the combination agent. Follow the dosing schedule, including the 3-day or 4-day dose ramp-up, as shown in Table 4. Start VENCLEXTA administration on Cycle 1 Day 1 in combination with: • Azacitidine 75 mg/m^2 intravenously or subcutaneously once daily on Days 1-7 of each 28- day cycle; OR • Decitabine 20 mg/m^2 intravenously once daily on Days 1-5 of each 28-day cycle; OR • Cytarabine 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle.	**ABBVIE SDN BHD** 9th Floor Menara Lien Hoe, No.8, Persiaran Tropicana, Tropicana Golf & Country Resort, 47410 Petaling Jaya, Selangor.

<table>
<tr><th>No.</th><th>Product
[Active Ingredient]</th><th>Additional Indication</th><th>Product Registration Holder (PRH)</th></tr>
<tr><td></td><td></td><td>
Table 4. Dosing Schedule for 3- or 4-Day Ramp-Up Phase in Patients with AML
<table>
<tr><th>Day</th><th colspan="2">Venclexta Oral Daily Dose</th></tr>
<tr><td>1</td><td colspan="2">100 mg</td></tr>
<tr><td>2</td><td colspan="2">200 mg</td></tr>
<tr><td>3</td><td colspan="2">400 mg</td></tr>
<tr><td>Days 4 and beyond</td><td>400 mg orally once daily of each 28-day cycle in combination with azacitidine or decitabine</td><td>600 mg orally once daily of each 28-day cycle in combination with low-dose cytarabine</td></tr>
</table>

Continue VENCLEXTA, in combination with azacitidine or decitabine or low-dose cytarabine, until disease progression or unacceptable toxicity.

Refer to Clinical Studies and Prescribing Information for azacitidine, decitabine, or cytarabine for additional dosing information.

Risk Assessment and Prophylaxis for Tumor Lysis Syndrome

Patients treated with Venclexta may develop TLS. Refer to the appropriate section below for specific details on management.

<u>Acute Myeloid Leukaemia</u>

Acute Myeloid Leukaemia
All patients should have white blood cell count less than 25 × 10^9/L prior to initiation of VENCLEXTA. Cytoreduction prior to treatment may be required.
</td><td></td></tr>
</table>

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
		• Prior to first VENCLEXTA dose, provide all patients with prophylactic measures including adequate hydration and anti-hyperuricemic agents and continue during ramp-up phase. • Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA. • Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up and 24 hours after reaching final dose. • For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase (LDH) levels, or reduced renal function), consider additional measures, including increased laboratory monitoring and reducing VENCLEXTA starting dose. **Dose Modifications Based on Toxicities** **Acute Myeloid Leukaemia** <u>Dose modification for other toxicities</u> Monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status. Dose modifications of VENCLEXTA for adverse reactions are provided in Table 5.	

<table>
<tr><th>No.</th><th>Product
[Active Ingredient]</th><th>Additional Indication</th><th>Product Registration Holder (PRH)</th></tr>
<tr><td></td><td></td><td>Table 5. Recommended VENCLEXTA Dosage Modifications for Adverse Reactions in AML
<table>
<tr><th>Adverse Reaction</th><th>Occurrence</th><th>Dosage Modification</th></tr>
<tr><td colspan="3">Hematologic Adverse Reactions</td></tr>
<tr><td>Grade 4 neutropenia with or without fever or
infection; or Grade 4 thrombocytopenia [see
Warnings and Precautions]</td><td>Occurrence prior to achieving remission[a]</td><td>In most instances, do not interrupt VENCLEXTA in combination with azacitidine, decitabine, or low-dose cytarabine due to cytopenias prior to achieving remission.</td></tr>
<tr><td></td><td>First occurrence after achieving remission and lasting at least 7 days</td><td>Delay subsequent cycle of VENCLEXTA in combination with azacitidine, decitabine, or low-dose cytarabine and monitor blood counts. Upon resolution to Grade 1 or 2, resume
VENCLEXTA at the same dose in combination with azacitidine, decitabine or low-dose cytarabine.</td></tr>
<tr><td></td><td>Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer</td><td>Delay subsequent cycle of VENCLEXTA in combination with azacitidine, or decitabine, or low-dose cytarabine and monitor blood counts.
Upon resolution to Grade 1 or 2, resume
VENCLEXTA at the same dose in combination with azacitidine, decitabine or low-dose cytarabine, and reduce
VENCLEXTA duration by 7 days</td></tr>
</table></td><td></td></tr>
</table>

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)

		during each of the subsequent cycles, such as 21 days instead of 28 days.
Non-Hematologic Adverse Reactions		
Grade 3 or 4 nonhematologic Toxicities [see Adverse Reactions]	Any occurrence	Interrupt VENCLEXTA if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume VENCLEXTA at the same dose.
[a]Recommend bone marrow evaluation.		

<table>
<tr><th>No.</th><th>Product
[Active Ingredient]</th><th>Additional Indication</th><th>Product Registration Holder (PRH)</th></tr>
<tr><td>2.</td><td>Lynparza 100 mg Film-Coated Tablets
[Olaparib 100mg]

Lynparza 150 mg Film-Coated Tablets
[Olaparib 150mg]</td><td>
INDICATION :

<u>Prostate cancer</u>
Lynparza is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic BRCA or ATM mutated metastatic castration resistant prostate cancer (mCRPC) who have progressed following prior treatment with a new hormonal agent (e.g. abiraterone or enzalutamide).

POSOLOGY :

<u>Patient Selection</u>
Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious BRCA mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).
Table 1 Biomarker Testing for Patient Selection
<table>
<tr><th rowspan="2">Indication</th><th rowspan="2">Biomarker</th><th colspan="2">Sample Type</th></tr>
<tr><th>Tumour</th><th>Blood</th></tr>
<tr><td>First-line maintenance treatment of BRCA-mutated advanced ovarian cancer*</td><td>BRCA1m, BRCA2m</td><td>X</td><td>X</td></tr>
<tr><td>Maintenance treatment of platinum-sensitive relapsed ovarian cancer</td><td>No requirement for biomarker
testing</td><td></td><td></td></tr>
<tr><td>First-line maintenance treatment of HRD-positive advanced ovarian cancer in combination with bevacizumab*</td><td>BRCA1m, BRCA2m and/or
genomic instability</td><td>X</td><td></td></tr>
</table>
</td><td>ASTRAZENECA SDN. BHD.
Level 11 & 12, Nucleus Tower, No. 10, Jalan PJU 7/6, Mutiara Damansara, 47800 Petaling Jaya, Selangor.</td></tr>
</table>

<table>
<tr><th>No.</th><th>Product
[Active Ingredient]</th><th>Additional Indication</th><th>Product Registration Holder (PRH)</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>gBRCA1/2-mutated HER2-negative metastatic breast cancer</td><td>gBRCA1m, gBRCA2m</td><td></td><td>X</td></tr>
<tr><td>First-line maintenance treatment of germline

BRCA-mutated metastatic pancreatic adenocarcinoma</td><td>gBRCA1m, gBRCA2m</td><td></td><td>X</td></tr>
<tr><td rowspan="2">Germline or somatic BRCA or ATM mutated metastatic castration-resistant prostate

cancer*</td><td>ATMm, BRCA1m, BRCA2m</td><td>X</td><td></td></tr>
<tr><td>gBRCA1m, gBRCA2m</td><td></td><td>X</td></tr>
</table>
* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test.

<u>Duration of treatment</u>

BRCA or ATM mutated Metastatic Castration-Resistant Prostate Cancer:

It is recommended that treatment be continued until disease progression or unacceptable toxicity.

Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.
</td><td></td></tr>
</table>

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
3.	Olumiant 2mg Film-Coated Tablets [Baricitinib 2mg] Olumiant 4mg Film-Coated Tablets [Baricitinib 4mg]	**INDICATION :** <u>Atopic Dermatitis</u> Olumiant is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy. **POSOLOGY :** <u>Atopic Dermatitis</u> The recommended dose of Olumiant is 4 mg once daily. A dose of 2 mg once daily is appropriate for patients such as those aged≥ 75 years and may be appropriate for patients with a history of chronic or recurrent infections. A dose of 2 mg once daily should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering. Olumiant can be used with or without topical corticosteroids. The efficacy of Olumiant can be enhanced when given with topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for sensitive areas only, such as the face, neck, intertriginous and genital areas. Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 8 weeks of treatment.	**ZUELLIG PHARMA SDN. BHD.** No. 15, Persiaran Pasak Bumi, Sek. U8, Perindustrian Bukit Jelutong, 40150 Shah Alam, Selangor.

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
4.	TREMFYA 100MG/ML SOLUTION FOR INJECTION [Guselkumab 100 mg/ml]	**INDICATION:** Psoriatic Arthritis Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. **POSOLOGY :** Psoriatic arthritis The recommended dose of Tremfya is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment.	**JOHNSON & JOHNSON SDN. BHD.** Lot 3 & 5, Jalan Tandang, 46050 Petaling Jaya, Selangor.

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
5.	ACCENTRIX 10MG/ML SOLUTION FOR INJECTION [Ranibizumab 10mg/ml]	**INDICATION:** Accentrix is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease. **POSOLOGY:** *[The proposed posology for this additional indication is reflected in those highlighted in **bold**, hence the full posology will read as follow:]* *Dosage regimen* *Single use vial (**adults and preterm infants**) for intravitreal use only. Use of more than one injection from a vial can lead to product contamination and subsequent ocular infection. Accentrix must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose for Accentrix **in adults** is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 mL. The interval between two doses injected into the same eye should **not be shorter than one month**.* *Treatment **in adults** is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME, PDR, and RVO, initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.* *If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Accentrix should be discontinued. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME.*	**NOVARTIS CORPORATION (MALAYSIA) SDN. BHD.** Level 22, Tower B, Plaza 33, No. 1, Jalan Kemajuan, Section 13, 46200 Petaling Jaya, Selangor.

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
		For PDR and RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly. *The treatment of visual impairment due to CNV should be determined individually per patient based on disease activity. Some patients may only need one injection during the first 12 months; others may need more frequent treatment, including a monthly injection. For CNV secondary to pathologic myopia (PM), many patients may only need one or two injections during the first year (see section CLINICAL PHARMACOLOGY).* *Ranibizumab and laser photocoagulation in DME and in macular oedema secondary to BRVO* *There is some experience of ranibizumab administered concomitantly with laser photocoagulation (see section PHARMACODYNAMICS). When given on the same day, ranibizumab should be administered at least 30 minutes after laser photocoagulation. ranibizumab can be administered in patients who have received previous laser photocoagulation.* *Ranibizumab and verteporfin photodynamic therapy in CNV secondary to PM* *There is no experience of concomitant administration of ranibizumab and verteporfin.* ***Preterm infants*** ***The recommended dose for Accentrix in preterm infants is 0.2 mg given as an intravitreal injection. This corresponds to an injection volume of 0.02 ml. In preterm infants treatment of ROP is initiated with a single injection per eye and may be given bilaterally on the same day. In total, up to three injections per eye may be administered within six months of treatment initiation if there are signs of disease activity. Most patients (78%) in the clinical study received one injection per eye. The administration of more than three injections per eye has not been studied. The interval between two doses injected into the same eye should be at least four weeks.*** *Special populations* *Hepatic impairment* *Ranibizumab has not been studied in patients with hepatic impairment. However, no special considerations are needed in this population.*	

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
		<u>Renal impairment</u> *Dose adjustment is not needed in patients with renal impairment (see section PHARMACOKINETICS).* *<u>Elderly</u>* *No dose adjustment is required in the elderly. There is limited experience in patients older than 75 years with DME.* *<u>Pediatric population</u>* *The safety and efficacy of ranibizumab in children and adolescents below 18 years of age* ***for indications other than retinopathy of prematurity*** *have not been established. Available data in adolescent patients aged 12 to 17 years with visual impairment due to CNV are described in section CLINICAL STUDIES but no recommendation on a posology can be made.* *<u>Method of administration</u>* *As with all medicinal products for parenteral use, Accentrix should be inspected visually for particulate matter and discoloration prior to administration. The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section CONTRAINDICATIONS). Adequate anesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection, in accordance with local practice. For information on preparation of Accentrix, see section INSTRUCTIONS FOR USE AND HANDLING.* ***In adults*** *the injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the center of the globe. The injection volume of 0.05 mL is then delivered; the scleral site should be rotated for subsequent injections.* ***In preterm infants, the injection needle should be inserted 1.0 to 2.0 mm posterior to the limbus with the needle pointing towards the optic nerve. The injection volume of 0.02 mL is then delivered****.*	

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
6.	Ozempic® 1.34 mg/ml (0.25 mg, 0.5 mg/dose) Solution for injection in pre-filled pen Ozempic® 1.34 mg/ml (1 mg/dose) Solution for injection in pre-filled pen [Semaglutide 1.34mg]	**INDICATION:** Prevention of cardiovascular events: Ozempic® is indicated to reduce the risk of major adverse cardiovascular events (MACE), composed of cardiovascular (CV) death, non-fatal myocardial infarction and non-fatal stroke, in adults with type 2 diabetes who have established CV disease or are at high risk for CV disease.	**NOVO NORDISK PHARMA (MALAYSIA) SDN. BHD.** Menara 1 Sentrum, Level 16, No. 201, Jalan Tun Sambathan, 50470 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur.

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
7.	Soliqua SoloStar 100units/mL+33mcg/mL solution for injection in a pre-filled pen [Insulin Glargine 100 Units/mL & Lixisenatide 33 mcg/Ml] Soliqua SoloStar 100units/mL+50mcg/mL solution for injection in a pre-filled pen [Insulin Glargine 100 Units/mL & Lixisenatide 50 mcg/mL]	**INDICATION:** Soliqua is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to metformin with or without SGLT-2 inhibitors. (For study results with respect to effect on glycaemic control, and the populations studied, see section "special warnings and precautions for use" and "pharmacodynamics properties"). **POSOLOGY:** Soliqua is available in two pens, providing different dosing options, i.e., Soliqua (10-40) pen, Soliqua (30-60) pen respectively. The differentiation between the pen strengths is based on the dose range of the pen. • Soliqua 100 units/ml + 50 micrograms/ml pre-filled pen delivers dose steps from 10-40 units of insulin glargine in combination with 5-20 mcg lixisenatide (Soliqua (10-40) pen). • Soliqua 100 units/ml + 33 micrograms/ml pre-filled pen delivers dose steps from 30-60 units of insulin glargine in combination with 10-20 mcg lixisenatide (Soliqua (30-60) pen). To avoid medication errors, the prescriber must make sure that the correct strength and number of dose steps is stated in the prescription. <u>Posology</u> The dose must be individualised based on clinical response and is titrated based on the patient's need for insulin. The lixisenatide dose is increased or decreased along with insulin glargine dose and also depends on which pen is used. <u>Starting dose</u> Therapy with basal insulin or glucagon-like peptide-1 (GLP-1) receptor agonist or oral glucose lowering medicinal product other than metformin and SGLT-2 inhibitors should be discontinued prior to initiation of Soliqua. The starting dose of Soliqua is based on previous anti-diabetic treatment, and in order not to exceed the recommended lixisenatide starting dose of 10 mcg:	**SANOFI-AVENTIS (MALAYSIA) SDN. BHD.** Unit TB-18-1, Level 18, Tower B, Plaza 33, No.1, Jalan Kemajuan, Seksyen 13, 46200 Petaling Jaya, Selangor.

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)

		Previous therapy		
		Insulin naïve patients (Oral anti-diabetic treatment or GLP-1 receptor agonist)	**Insulin glargine (100 units/ml)** ≥20 to <30 units**	**Insulin glargine (100 units/ml)** ≥30 to ≤60 units**
Starting dose and pen	**Soliqua (10-40) pen**	10 dose steps (10 units/5 mcg)*	20 dose steps (20 units/10 mcg)*	
	Soliqua (30-60) pen			30 dose steps (30 units/10 mcg)*

* units insulin glargine (100 units/ml) / mcg lixisenatide

** If a different basal insulin was used:

- For twice daily basal insulin or insulin glargine (300 units/ml), the total daily dose previously used should be reduced by 20% to choose the Soliqua starting dose.
- For any other basal insulin the same rule as for insulin glargine (100 units/ml) should be applied

The maximum daily dose is 60 units insulin glargine and 20 mcg lixisenatide corresponding to 60 dose steps.

Soliqua should be injected once a day within one hour prior to a meal. It is preferable that the prandial injection is performed before the same meal every day, when the most convenient meal has been chosen.

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
		Dosage titration Soliqua is to be dosed in accordance with the individual patient's need for insulin. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose. Close glucose monitoring is recommended during the transfer and in the following weeks. • If the patient starts with the Soliqua (10-40) pen, the dose may be titrated up to 40 dose steps with this pen. • For doses >40 dose steps/day titration must be continued with Soliqua (30-60) pen. • If the patient starts with the Soliqua (30-60) pen, the dose may be titrated up to 60 dose steps with this pen. • For total daily doses >60 dose steps/day, Soliqua must not be used. Patients adjusting the amount or timing of dosing should only do so under medical supervision with appropriate glucose monitoring. Special population Elderly (≥65 years old) Soliqua can be used in elderly patients. The dose should be adjusted on an individual basis, based on glucose monitoring. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements. For lixisenatide no dose adjustment is required based on age. The therapeutic experience of Soliqua in patients ≥75 years of age is limited. Renal impairment Soliqua is not recommended in patients with severe renal impairment and end-stage renal disease as there is no sufficient therapeutic experience with use of lixisenatide. No dose adjustment is required for lixisenatide in patients with mild or moderate renal impairment.	

No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
		In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism. In patients with mild to moderate renal impairment using Soliqua, frequent glucose monitoring and dose adjustment may be necessary. Hepatic impairment No dose adjustment of lixisenatide is needed in patients with hepatic impairment. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism. Frequent glucose monitoring and dose adjustment may be necessary for Soliqua in patients with hepatic impairment. Paediatric population There is no relevant use of Soliqua in the paediatric population. <u>Method of administration</u> Soliqua is to be injected subcutaneously in the abdomen, deltoid, or thigh. The injection sites should be rotated within the same region (abdomen, deltoid, or thigh) from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. Patients should be instructed to always use a new needle. The re-use of insulin pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the instructions described in the Instructions for Use accompanying the package leaflet. Soliqua must not be drawn from the cartridge of the pre-filled pen into a syringe to avoid dosing errors and potential overdose.	