Arden and Greater East Midlands Commissioning Support Unit

Arden and Greater East Midlands Commissioning Support Unit in association with
Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services,
United Lincolnshire Hospitals Trust and Lincolnshire Partnership Foundation Trust

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 9; Number 7 **April 2015**

What's new this month?

- ***Dymista*** **nasal spray, a combination antihistamine (azelastine hydrochloride) and corticosteroid (fluticasone propionate) nasal spray licensed for the treatment of perennial and seasonal allergic rhinitis, has been reviewed and continues to be designated RED-RED (see page 3).**
- **Guidance on the use of intranasal corticosteroids in perennial and seasonal allergic rhinitis has been updated. Beclometasone 50 microgram nasal spray (generic/*Beconase*) remains the preferred first line product; alternative second and third line options are also defined (see page 5).**
- **Dabigatran etexilate (*Pradaxa*) has been approved by NICE for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the prevention of recurrent DVT and PE in adults. The product is now approved for use for these indications through the *Lincolnshire Joint Formulary* and is designated GREEN. Local guidance will be updated to reflect this and will appear in the *PACE Bulletin* later in the year (see page 5).**
- **PACEF previously reviewed the safety of the tiotropium *Spiriva Respimat* device after a pooled analysis of a number of trials showed an association between *Respimat* use and excess mortality and cardiovascular death, particularly in patients with a history of cardiac arrhythmias. This contrasted with the findings of studies using tiotropium *Handihaler* which had been shown to be associated with a reduction in all-cause mortality compared to placebo. Following publication of the results of the TIOSPIR trial in the *New England Journal of Medicine* in 2013, PACEF reviewed the findings of the trial and were satisfied that any safety concerns relating to the use of the *Respimat* device had been sufficiently investigated and resolved. As a result of this, both the *Spiriva HandiHaler* and the *Spiriva Respimat* devices are designated GREEN and both products are included in the *Lincolnshire Joint Formulary*. The publication of a MHRA drug safety review has confirmed existing PACEF advice and concluded that there is no difference in the risk of cardiovascular events between the two devices. Nonetheless, the MHRA remind prescribers that tiotropium must be used with caution in patients with certain cardiac conditions (see page 6).**
- **New legislation around drugs and driving is reviewed (see page 7).**
- **Further incidents have occurred in Lincolnshire related to the inadvertent prescribing of zuclopenthixol acetate injection (*Clopixol Acuphase*) to patients intended to receive zuclopenthixol decanoate injection (*Clopixol Depot*/*Clopixol Conc*). Zuclopenthixol acetate injection (*Clopixol Acuphase*) is designated RED and should only be prescribed through specialist mental health services and confined within secondary care. All requests to GPs to prescribe zuclopenthixol acetate or *Clopixol Acuphase* should be refused. All requests to prescribe an unspecified salt of zuclopenthixol should be clarified and confirmed as decanoate. All prescriptions for zuclopenthixol acetate or *Clopixol Acuphase* presented to a community pharmacy or to GP dispensary staff are likely to have been issued in error and should be verified with the prescriber. Within this context, zuclopenthixol acetate injection 50mg/ml (*Clopixol Acuphase*) is designated RED. Please do not prescribe, supply or administer in primary care. Zuclopenthixol decanoate injection 200mg/ml (*Clopixol Injection*) and 500mg/ml**

(*Clopixol Conc*) is designated AMBER without shared care and can be prescribed for depot antipsychotic maintenance treatment within license (see page 8).

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SUMMARY OF PACEF DECISIONS: *MARCH 2015 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Beclometasone 50 microgram nasal spray (generic/*Beconase*) (generic/GlaxoSmithKline)	For perennial and seasonal allergic rhinitis. Vasomotor rhinitis.	GREEN First line. Included in the *Lincolnshire Joint Formulary*.
Budesonide 64 microgram nasal spray (generic/*Rhinocort Aqua*) (generic/AstraZeneca)	For perennial and seasonal allergic rhinitis. Nasal polyps.	GREEN Second line. Included in the *Lincolnshire Joint Formulary*.
Dabigatran etexilate 110mg and 150mg capsules (*Pradaxa*) (Boehringer Ingelheim)	Treatment of DVT and pulmonary embolism (PE) and the prevention of recurrent DVT and PE (110mg and 150mg capsule only)	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* for these indications.
Fluticasone furoate 27.5 microgram nasal spray (*Avamys*) (GlaxoSmithKline)	Allergic rhinitis	GREEN Third line. Included in the *Lincolnshire Joint Formulary*.
Fluticasone propionate/ azelastine hydrochloride 50 microgram/ 137 microgram nasal spray (*Dymista*) (Meda)	For perennial and seasonal allergic rhinitis.	RED-RED Still not approved for inclusion in the *Lincolnshire Joint Formulary*
Fluticasone propionate 50 microgram nasal spray (*Flixonase*) (GlaxoSmithKline)	For perennial and seasonal allergic rhinitis.	RED-RED Not included in the *Lincolnshire Joint Formulary.*
Tiotropium bromide 18 microgram capsule and *Spiriva Handihaler* (Boehringer Ingelheim)	Maintenance treatment of chronic obstructive pulmonary disease (COPD).	GREEN Included in the *Lincolnshire Joint Formulary.*
Tiotropium 2.5 microgram per dose *Spiriva Respimat* (60 dose) (Boehringer Ingelheim)	Maintenance treatment of chronic obstructive pulmonary disease (COPD). Add-on maintenance treatment of asthma in patients receiving inhaled corticosteroids and long acting beta 2 agonists with $\geq$ 1 severe exacerbation in previous year.	GREEN Included in the *Lincolnshire Joint Formulary.*
Zuclopenthixol acetate Injection 50mg/ml (*Clopixol Acuphase*) (Lundbeck)	Licensed for the initial treatment of acute psychoses including mania and exacerbations of chronic psychoses, particularly where a rapid onset of action and a duration of effect of two to three days is desirable. This preparation is usually used in hospital for an *acute episode* and should not be confused with depot preparations which are used in the community or clinics for *maintenance* treatment.	RED Included in the *Lincolnshire Joint Formulary f*or LPFT use only.

Zuclopenthixol decanoate injection 200mg/ml (*Clopixol Injection*) and 500mg/ml (*Clopixol Conc*) (Lundbeck)	Psychosis, especially schizophrenia. This preparation is used for *maintenance* treatment and should not be used for the short-term management of an *acute episode*.	AMBER without shared care. Included in the *Lincolnshire Joint Formulary.*

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the PACEF website (http://lincolnshire-pacef.nhs.uk); follow the commissioning link to PACEF. Electronic copies of the *PACE Bulletin* are circulated to a wide readership via email. If you are not currently on our distribution list and wish to receive regular copies of PACEF publications please contact Sandra France on sandra.france@gemcsu.nhs.uk.

Google searching can be a quick and effective way of finding back numbers of the *PACE Bulletin* relevant to a specific topic of interest. Searchers are advised to use the official version of the *Bulletin* available from the PACEF website rather than depend on a potentially unreliable draft or variant found through Google or an alternative search engine.
The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

REVIEW: FLUTICASONE PROPIONATE/AZELASTINE HYDROCHLORIDE 50 MICROGRAM/137 MICROGRAM NASAL SPRAY (*DYMISTA*)

This is an updated version of a New Drug Assessment that originally appeared in *PACE Bulletin* Volume 7 No 12 (July 2013)

Dymista nasal spray is a combination antihistamine (azelastine hydrochloride) and corticosteroid (fluticasone propionate) nasal spray. It holds a UK marketing authorisation for perennial and seasonal allergic rhinitis.

PACEF reviewed a meta-analysis of three trials comparing the fluticasone/azelastine combination nasal spray with the individual components and placebo in 3,398 adults and adolescents with moderate to severe seasonal allergic rhinitis. From these combined results the fluticasone/azelastine combination emerged as significantly superior to placebo and to fluticasone propionate or azelastine hydrochloride prescribed as monotherapy in terms of reduced nasal and ocular symptom scores. All three active treatments were significantly better than placebo.

In a second smaller scale randomized controlled trial, the fluticasone/azelastine combination nasal spray emerged as significantly superior to separate components and placebo in terms of total nasal symptom score. Both the meta-analysis and the trial reflect short-term use (14 days) leaving unresolved questions around longer-term efficacy and safety. A post hoc analysis of the results of one of the pivotal trials, undertaken after PACEF published its original NDA, concludes that *Dymista* is superior to its active components in terms of more effective symptom control and faster onset of action.

There is no data comparing *Dymista* against any other intranasal preparations or any oral antihistamine. However, evidence from two small trials has shown that combination oral antihistamine and intranasal corticosteroid use in allergic rhinitis offers no more benefit in terms of symptom control than an intranasal steroid used alone. *Dymista* was not used as a comparator in either of these trials, although one of them compared the intranasal steroid component in *Dymista* (fluticasone propionate) with intranasal fluticasone propionate plus oral levocetirizine. In the other trial, mometasone nasal spray alone was compared to mometasone nasal spray plus oral loratadine.

The main adverse effects associated with the use of *Dymista* are epistaxis, headache, unpleasant taste and unpleasant smell sensations.

An updated cost comparison reveals that, despite a significant price reduction in January 2015 (21.7%), *Dymista* still remains expensive in comparison to intranasal cortiocosteroids and oral antihistamines, although lower cost than the individual components prescribed separately:

Drug	Daily dose	Cost (£) (doses)
Fluticasone propionate/ azelastine hydrochloride 50 microgram/ 137 microgram nasal spray (*Dymista*)	1 spray into each nostril twice daily	£ 14.80 (120)
Azelastine hydrochloride 0.1% nasal spray (*Rhinolast*)	1 spray into each nostril twice daily	£10.50 (150)
Fluticasone propionate 50 microgram nasal spray (*Flixonase*)	1 spray into each nostril twice daily	£11.01 (150)
Beclometasone 50 microgram nasal spray (generic)	2 sprays into each nostril twice daily	£2.58(200)
Beclometasone 50 microgram nasal spray (*Beconase*)	2 sprays into each nostril twice daily	£2.19(200)
Beclometasone 50 microgram nasal spray (*Nasobec*)	2 sprays into each nostril twice daily	£3.06 (200)
Budesonide 64 microgram nasal spray (generic)	1 spray into each nostril twice daily	£3.85 (120)
Budesonide 64 microgram nasal spray (*Rhinocort Aqua*)	1 spray into each nostril twice daily	£3.49 (120)
Fluticasone furoate 27.5 microgram nasal spray (*Avamys*)	2 sprays into each nostril once daily reducing to 1 spray each nostril daily.	£6.44 (120)
Mometasone 50 microgram nasal spray (Nasonex)	2 sprays into each nostril once daily	£7.68 (140)
Triamcinolone acetonide 55 microgram nasal spray (*Nasacort*)	2 sprays per nostril once daily	£7.39 (120)
Sodium cromoglicate 4% nasal spray (*Rynacrom Spray*)	1 spray into each nostril two to four times a day	£17.07 (22ml)

Drug	Daily dose	Cost (30 days)
Cetirizine 10mg tablets	One tablet daily	£1.08
Loratadine 10mg tablets	One tablet daily	£1.10

PACEF Recommendations:

PACEF remain concerned about the lack of trial data comparing *Dymista* with a nasal corticosteroid plus an oral antihistamine (e.g. loratadine 10mg tablets or cetirizine 10mg tablets). Since we last assessed this product in July 2013, the only additional evidence worthy of consideration has been a post hoc analysis of existing data plus two small trials, neither of which used *Dymista* as an active comparator. On examination, none of this additional evidence was sufficiently compelling to change the conclusion of our assessment. PACEF remain concerned about the lack of long-term efficacy and safety data and even the recent price reduction has not been sufficient to allay our concerns about the prohibitively high cost of *Dymista* in comparison to lower cost alternatives. As a result of this, fluticasone propionate/ azelastine hydrochloride 50 microgram/ 137 microgram nasal spray (*Dymista*) remains RED-RED and is not approved for inclusion in the *Lincolnshire Joint Formulary*.

UPDATE: *THE USE OF INTRANASAL CORTICOSTEROIDS IN PERENNIAL AND SEASONAL ALLERGIC RHINITIS*

- Beclometasone 50 microgram nasal spray (generic/*Beconase*) is the lowest cost intranasal corticosteroid and remains the first line product of choice.
- Combination therapy with an oral antihistamine, such as cetirizine 10mg or loratadine 10mg, is significantly lower in cost than *Dymista*.
- Budesonide 64 microgram nasal spray (generic or *Rhinocort Aqua*) is also comparatively low cost and represents an appropriate second line choice that would still be low cost in combination with an oral antihistamine.
- Fluticasone furoate 27.5 microgram nasal spray (*Avamys*) is an appropriate third line nasal steroid in preference to more expensive products such as mometasone 50 microgram nasal spray (*Nasonex*), triamcinolone acetonide 55 microgram nasal spray (*Nasacort*) and fluticasone propionate 50 microgram nasal spray (*Flixonase*).
- Where a fluticasone preparation is indicated fluticasone furoate nasal spray (*Avamys*) should be preferred.
- Fluticasone propionate 50 microgram nasal spray (*Flixonase*) is prohibitively expensive in comparison to alternative intranasal corticosteroid preparations and should no longer be initiated in new patients. Existing patients can continue on *Flixonase* until they or their clinician consider it to be appropriate to stop or change to a lower cost alternative. For new patients, fluticasone propionate 50 microgram nasal spray (*Flixonase*) should be considered to be RED-RED.

NICE TECHNOLOGY APPRAISAL 327: *DABIGATRAN ETEXILATE FOR THE TREATMENT AND SECONDARY PREVENTION OF DEEP VEIN THROMBOSIS AND/OR PULMONARY EMBOLISM* (DECEMBER 2014)

Dabigatran etexilate is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults.

Notes

Dabigatran etexilate (*Pradaxa*) is now licensed for the treatment of DVT and PE and the prevention of recurrent DVT and PE in adults. The recommended dose is 300mg (150mg twice daily) following treatment with a parenteral anticoagulant for at least 5 days. For people aged 80 or older and for people having verapamil the recommended dose is 220mg (110mg twice daily). In people aged 75-80 years, people with moderately reduced kidney function, people with gastritis, esophagitis or gastroesophageal reflux, and people at increased risk bleeding, either dose (300mg or 220mg) can be given based an individual assessment. Dabigatran etexilate is contraindicated in people with severely reduced kidney function. Only the 110mg and 150mg capsule formulations of *Pradaxa* hold a marketing authorisation for these indications.

Existing PACEF *Guidance on the use of rivaroxaban (Xarelto) for the treatment of DVT and the prevention of recurrent DVT and PE* (*PACE Bulletin* Vol 7 No 15 (August 2013)) will be updated and expanded to include dabigatran etexilate.

PACEF Recommendation:
Dabigatran etexilate (*Pradaxa*) has been approved by NICE for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the prevention of recurrent DVT and PE in adults. The product is now approved for use for these indications through the *Lincolnshire Joint Formulary* and is designated GREEN. Local guidance will be updated to reflect this and will appear in the *PACE Bulletin* later in the year.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA): *DRUG SAFETY UPDATE* (FEBRUARY 2015)

TIOTROPIUM DELIVERED VIA RESPIMAT COMPARED WITH HANDIHALER: NO SIGNIFICANT DIFFERENCE IN MORTALITY IN TIOSPIR TRIAL

Tiotropium (*Spiriva*) is licensed as a maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD). It is available in two different inhaler devices:

- the *Spiriva HandiHaler* (from a capsule containing 18 micrograms of tiotropium bromide).
- the soft-mist *Spiriva Respimat* inhaler (taken as two puffs once daily (2.5 micrograms of tiotropium delivered per puff)).

Previous studies of tiotropium suggested that more people died while using tiotropium *Respimat* compared with placebo and with tiotropium *HandiHaler*. This was reported in the MHRA Drug Safety Update in November 2011. As a result of this standard advice was to use the tiotropium *Respimat* device with caution in patients with known cardiac rhythm disorders.

TIOSPIR clinical trial

The TIOSPIR trial compared the safety and efficacy of tiotropium delivered via *Respimat* (2.5 micrograms or 5 micrograms once daily) with tiotropium delivered via *HandiHaler* (18 micrograms once daily). The trial included 17,135 participants with COPD who were followed up for a mean of 2.3 years. The primary safety outcome was the time to death from any cause, which was used to calculate the relative risk of death between groups. The primary efficacy outcome was time to first exacerbation of COPD. Cardiovascular safety was also assessed.

Results

- There was no significant difference in the risk of death from any cause between tiotropium *Respimat* (5 micrograms or 2.5 micrograms) compared with tiotropium *HandiHaler* (tiotropium 18 micrograms)
- For Respimat 5mcg vs Handihaler 18mcg the hazard ratio was 0. 96.
- The incidences of different causes of death (including death due to cardiovascular events) and incidences of major cardiovascular adverse events were similar across the three groups.
- There was no significant difference in the time to first exacerbation of COPD between tiotropium *Respimat* 5 micrograms and tiotropium *HandiHaler* 18 micrograms; hazard ratio, 0.98.
- In participants with previous cardiac arrhythmia there was no significant difference in the risk of death from any cause between tiotropium *Respimat* 5mcg and tiotropium *Handihaler* 18mcg; hazard ratio 0.81.

MHRA advice to healthcare professionals

When using tiotropium delivered via *Respimat* or *Handihaler* to treat COPD:

- take the risk of cardiovascular side effects into account for patients with conditions that may be affected by the anticholinergic action of tiotropium, including those with:
  - myocardial infarction in the last 6 months.
  - unstable or life threatening cardiac arrhythmia.
  - cardiac arrhythmia requiring intervention or a change in drug therapy in the past year.

  - hospitalisation for heart failure (NYHA Class III or IV) within the past year.
- Tell these patients to report any worsening of cardiac symptoms after starting tiotropium; patients with these conditions were excluded from clinical trials of tiotropium, including TIOSPIR.
- Review the treatment of all patients already taking tiotropium as part of the comprehensive management plan to ensure that it remains appropriate for them; regularly review treatment of patients at high risk of cardiovascular events.
- Remind patients not to exceed the recommended once daily dose.
- Continue to report suspected side effects to tiotropium or any other medicine on a Yellow Card: www.gov.uk/yellowcard

PACEF comment

PACEF previously reviewed the safety of the tiotropium *Spiriva Respimat* device after a pooled analysis of a number of trials showed an association between *Respimat* use and excess mortality and cardiovascular death, particularly in patients with a history of cardiac arrhythmias. This contrasted with the findings of studies using tiotropium *Handihaler* which had been shown to be associated with a reduction in all-cause mortality compared to placebo. Following publication of the results of the TIOSPIR trial in the *New England Journal of Medicine* in 2013, PACEF reviewed the findings of the trial and were satisfied that any safety concerns relating to the use of the *Respimat* device had been sufficiently investigated and resolved. As a result of this, both the *Spiriva HandiHaler* and the *Spiriva Respimat* devices are designated GREEN and both products are included in the *Lincolnshire Joint Formulary*. The publication of this MHRA drug safety review has confirmed existing PACEF advice and concluded that there is no difference in the risk of cardiovascular events between the two devices. Nonetheless, the MHRA remind prescribers that tiotropium must be used with caution in patients with certain cardiac conditions

NEW DRUGS AND DRIVING LEGISLATION

Currently, Section 4 of the Road Traffic Act 1988 includes an offence of driving whilst impaired through drugs, regardless of whether or not the drugs are being used legitimately. This means that if a patient's driving is found to be impaired by medicines, even if he or she is taking them as prescribed or as recommended in the product information, he or she may still be prosecuted. A new additional offence of driving with certain specified drugs in excess of specified levels came into force on 2nd March 2015 in England and Wales. The legislation also provides for a statutory 'medical defence' for patients taking their medicines as prescribed or in accordance with product information.

Roadside drug screening devices will use saliva to identify if a driver has taken one of a specified list of drugs (see below). The first group are commonly abused drugs for which low limits have been set; the second group are mainly licensed medicines that have a significant risk of being abused. The specified limits for the second group have been set higher than those in the first group and regular medical use of these products at licensed doses is unlikely to exceed these limits.

First group	Second group
Cannabis (THC)	Clonazepam
MDMA (ecstasy)	Diazepam
Ketamine	Lorazepam
Methylamfetamine	Oxazepam
Cocaine (and a cocaine metabolite BZE)	Temazepam
Lysergic acid diethylamide (LSD)	Flunitrazepam
Heroin/diamorphine metabolite (6-MAM)	Methadone

	Morphine

Where a drug from the Second group is detected by the police to be in excess of specified limits and there is evidence that the drug is being taken in accordance with instructions from a healthcare professional and/or the accompanying patient information leaflet the patient will have a legitimate 'medical defence' as long as their driving is not impaired. Where the patient's driving is impaired, an offence will have been committed even if the patient is taking the medicine is accordance with advice from a healthcare professional.

Advice for patients is as follows:

- **Do not drive if you feel sleepy, dizzy, are unable to concentrate or make decisions, have slowed thinking or if you experience sight problems.**
- **If you are taking a medicine that could affect your driving ability, do not drive until you know how the medicine affects you; this is particularly important when starting a new medicine or following a dose change. It is the responsibility of all drivers to ensure that when they are driving they are not impaired by medicines.**
- **Alcohol taken in combination with medicines, even in small amounts, can greatly increase the risk of accidents. Other medicines can also enhance the impairment associated with these specified drugs; ask you pharmacist or GP for more information.**
- **An untreated medical condition may itself cause driving impairment; do not stop taking your medicines without taking advice from your doctor.**
- **There is new legislation in place which places limits on the amounts of certain drugs that you can have in your bloodstream whilst driving. There is a 'medical defence' for those who are taking medicines in line with the advice of a healthcare professional, provided their driving is not impaired.**
- **Keep suitable evidence with you when driving to show that you are taking your medicine as prescribed or supplied by a healthcare professional (e.g. a repeat prescription slip or patient information leaflet).**

FURTHER CONFUSION BETWEEN ZUCLOPENTHIXOL ACETATE INJECTION (*CLOPIXOL ACUPHASE*) AND ZUCLOPENTHIXOL DECANOATE INJECTION (*CLOPIXOL*) IN LINCOLNSHIRE PRIMARY CARE

Further incidents have occurred in Lincolnshire related to the inadvertent prescribing of zuclopenthixol acetate injection (*Clopixol Acuphase*) to patients intended to receive zuclopenthixol decanoate injection (*Clopixol Depot*/*Clopixol Conc*). Zuclopenthixol acetate injection (*Clopixol Acuphase*) is designated RED and should only be prescribed through specialist mental health services and confined within secondary care. All requests to GPs to prescribe zuclopenthixol acetate or *Clopixol Acuphase* should be refused. All requests to prescribe an unspecified salt of zuclopenthixol should be clarified and confirmed as decanoate. All prescriptions for zuclopenthixol acetate or *Clopixol Acuphase* presented to a community pharmacy or to GP dispensary staff are likely to have been issued in error and should be verified with the prescriber. Within this context, zuclopenthixol acetate injection 50mg/ml (*Clopixol Acuphase*) is designated RED. Please do not prescribe, supply or administer this in primary care. Zuclopenthixol decanoate injection 200mg/ml (*Clopixol Injection*) and 500mg/ml (*Clopixol Conc*) is designated AMBER without shared care and can be prescribed for depot antipsychotic maintenance treatment within license.

Acknowledgements

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Stephen Gibson
Head of Prescribing and Medicines Optimisation (Lincolnshire)
Arden GEM Commissioning Support Unit

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