

BRIDGING CLINICAL PRACTICE  
AND REGULATION:  
BIOAVAILABILITY OF LAI AND  
OTHER MR ANTIPSYCHOTICS IN  
LIGHT OF EMA GUIDELINES

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# ANTIPSYCHOTIC MEDICINES

- Antipsychotic medication mainly treat psychosis but not only; they are important in treating other conditions too (depressive disorders, dementia, etc.)
- The first-generation antipsychotic (e.g. chlorpromazine, haloperidol, perphenazine, etc ) block the way brain uses several neurotransmitters especially dopamin; the newer, second-generation antipsychotic, have more complex mechanism of action: they block serotonin and dopamine receptors but they also may activate neurotransmitters
- Examples of second-generation antipsychotic : aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, ziprasidone, paliperidone, risperidone
- NEXT-generation antipsychotic medicines: xanomeline and trospium chloride combination (Cobenfy™) have a different mechanism of action as they do not impact dopamine; they only target acetylcholine receptors



# RISKS OF SIDE EFFECTS IN ANTIPSYCHOTIC THERAPY

- THE HIGHEST RISKS WERE ENCOUNTERED WITH THE FIRST-GENERATION ANTIPSYCHOTIC
- BETTER TOLERATED: SECOND-GENERATION ANTIPSYCHOTIC
- LEAST ADVERSE EVENTS EXPECTED WITH THE NEWEST GENERATION WHO LACK THE SLEEPINESS EFFECT AND HAVE LESS IMPACT ON THE MOTOR FUNCTION AND CARDIOVASCULAR SYSTEM



# SECOND GENERATION ANTIPSYCHOTIC (SGA) ADVERSE EVENTS

Second-generation antipsychotics (SGAs) are generally associated with fewer extrapyramidal symptoms than first-generation agents

SGAs have a reduced risk of tardive dyskinesia

BUT might have more important metabolic effects

# SECOND GENERATION ANTIPSYCHOTIC (SGA) ADVERSE EVENTS – CONTINUED

- **Metabolic disturbances:** weight gain, dyslipidemia, hyperglycemia, and increased risk of type 2 diabetes
- **Cardiovascular risks:** QT prolongation, orthostatic hypotension, tachycardia
- **Neurological effects:** sedation, dizziness, lowered seizure threshold; **extrapyramidal symptoms**
- **Endocrine effects:** hyperprolactinemia (notably with risperidone and paliperidone)
- **Other effects:** anticholinergic symptoms (dry mouth, constipation, blurred vision), sexual dysfunction, and in rare cases agranulocytosis



NEXT  
GENERATION  
ANTIPSYCHOTIC  
(COBENFY™)

Can cause urinary retention, increased heart rate, decreased gastric movement or angioedema

There is a risk of liver damage BUT does not prolong the QT interval to any clinically relevant extent !

The most common side effects of Cobenfy are nausea, indigestion, constipation, vomiting, hypertension, abdominal pain, diarrhoea, tachycardia, dizziness and gastroesophageal reflux disease  
(GENERAL ANTICHOLINERGIC SIDE EFFECTS)

DESPITE THE  
ADVERSE  
EVENTS  
ENCOUNTERED  
THE SECOND  
GENERATION IS  
THE MOST USED  
NOWADAYS

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ALTHOUGH THEY ARE SECOND-GENERATION THEIR PATENTS STARTED TO  
EXPIRE SOME YEARS AGO  
AND CONTINUE TO DO SO →

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CONSEQUENTLY : GENERIC ANTIPSYCHOTIC MEDICINES ARE DEVELOPED  
BY MANY PHARMACEUTICAL COMPANIES  
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BIOAVAILABILITY/BIOEQUIVALENCE STUDIES NEED TO BE PERFORMED  
FOR THESE MOLECULES OFTEN DEVELOPED AS LONG ACTING PRODUCTS  
(TO INCREASE PATIENTS ADHERENCE TO TREATMENT)

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SO,  
THE QUESTIONS IS HOW ? WHICH POPULATION, WHICH DESIGN, HOW  
TO PRESERVE PARTICIPANTS SAFETY, HOW TO OBTAIN INFORMED  
CONSENT ? AND THESE ARE ONLY SOME OF THE MANY QUESTIONS.....

# PHARMACEUTICAL FORMS

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SEVERAL PHARMACEUTICAL FORMS ARE PREFERRED DUE TO BETTER ADHERENCE OF THE PATIENTS TO THE TREATMENT :

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MODIFIED RELEASE ORAL PRODUCTS

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TRANSDERMAL PRODUCTS (TRANSDERMAL PATCHES)

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LONG ACTING INJECTIONS (I.M. DEPOT INJECTIONS):  
EVERY 1 MONTH OR EVERY 3 MONTHS ADMINISTRATION

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But, many immediate release products are still in use; MANY TREATMENT PLANS START WITH immediate release products followed by long acting ones

# WHAT EMA GUIDELINES RECOMMEND FOR LAI AND MR ANTIPSYCHOTICS ?

## SOME EXAMPLES OF EMA PRODUCT-SPECIFIC GUIDANCES:

Asenapine 5 mg and 10 mg sublingual tablets – Product specific BE guidance  
EMA/151690/2025 Rev. 1\*  
Adopted 12 May 2025

Population: Healthy volunteers or patients in case of intolerability

Study design: single dose, cross over, fasting

# PRODUCT SPECIFIC EMA BE GUIDANCE – II

PALIPERIDONE PALMITATE DEPOT  
SUSPENSION FOR INJECTION (EVERY  
3 MONTHS) PRODUCT SPECIFIC  
BIOEQUIVALENCE GUIDANCE, 175  
MG – 525 mg,  
EMA/CHMP/890768/2022, DATE OF  
COMING INTO EFFECT 1<sup>ST</sup> OF  
FEBRUARY 2025 (first draft dates  
from 2017)

Population: “Single dose studies in patients are not considered feasible as the patients need to be stabilised with a 1-month depot injection before administering the 3-month depot. Single dose studies in healthy volunteers are controversial due to the safety profile and the prolonged action of this product. In addition, the need for single dose data to capture the initial release of paliperidone is limited, as patients already have steady state paliperidone plasma levels at the start of treatment with this formulation.”

Study design: cross over or parallel, multiple dose study, **in patients**. BE to be based on paliperidone levels in plasma

# PRODUCT SPECIFIC EMA BIOEQUIVALENCE GUIDANCE III

- **Aripiprazole, cariprazine, olanzapine, brexpiprazole – no EMA product specific guidance is available for bioequivalence (BE) studies on these products.**
- **Quetiapine: According to the Question and Answer document concerning Quetiapine Lambda, 200–400 mg, the recommendations are as follows:**
  - Single-dose (SD) studies under both fasting and fed conditions in healthy volunteers for the 200 mg formulation**
  - Multiple-dose (MD) study for the 400 mg formulation in patients**
- **Xanomeline and trospium chloride combination (next-generation antipsychotic) – no specific product guidance is currently available. The originator product is still under extended clinical phase 3 study/ies in EU**

# US-FDA

- **Brexpiprazole** – draft Guidance available, October 2024 – Single dose study, cross over or parallel design (long thalf), fasting, in healthy males and non-pregnant, non-lactating females
- **Cariprazine** – draft Guidance available, October 2024 – Single dose study , cross over, fasting, in healthy males and non-pregnant, non-lactating females
- **Olanzapine** – draft Guidance available, Ocotber 2024 for immediate release product – Single dose study, cross over, fasting, in healthy males and non-pregnant, non-lactating females
- **Olanzapine** (pamoate) Extended Release Suspension for I.M. injection, Drat Guidance January 2016 – Multiple Dose study, parallel or cross over design, patients
- **Xanomeline** and trospium chloride – No specific Guidance as yet (the originator product is on the US market only since 2024)

# PRACTICAL EXPERIENCE: BIOEQUIVALENCE STUDIES FOR LAI AND OTHER MR SECOND GENERATION ANTIPSYCHOTICS

- Performed in healthy volunteers males and non-pregnant, non lactating women
- LAI: PALIPERIDONE, RISPERIDONE, ARIPIPRAZOLE
- ORAL MR : QUETIAPINE
- TRANSDERMAL: ASENAPINE
- TO COME: BRESPIRAZOLE ORAL MR PRODUCT, EVERY 7 DAYS ADMINISTRATION

# RISK ASSESSMENT LAI, OTHER MR FORMS OF SGA

## RISKS CLASSIFIED AS Medium and high – mitigation measures required

- **Safety related** : Adverse events such QT prolongation, orthostatic hypotension, extrapyramidal syndrom (although less than first-generation, could not be totally excluded), wheight gain
- **PK related**: standardization, inter-subjects variability
- **SAFETY & PK related**: **dumping effect** - large amount of the drug is released too quickly instead of being slowly released over week/s or months as intended !
- Because of the long duration of the study: **drop out/withdrawal rate**

# MITIGATION MEASURES TAKEN FOR SAFETY RELATED RISKS

- FOR LAI: From the beginning parallel design was chosen – each participant received thus only one dose from a LAI in one occasion only
- Choice of the **exclusion criteria**, e.g. :
  - candidates with abnormal QT interval, abnormal values of blood pressure measured in 2 positions, one being the standing position, abnormal Heart Rate were excluded from being enrolled in the study;
  - History of Psychiatric disease/s;
  - Actual Psychiatric conditions – psychiatric exam at screening;
- THEN →



## MITIGATION MEASURES TAKEN FOR SAFETY RELATED RISKS –CTD.

**TOLERANCE TESTING TO RISPERIDONE, PALIPERIDONE AND ARIPIPRAZOLE BY INTRODUCING A STAGE II SCREENING IN WHICH :**

**ORAL RISPERIDONE OR PALIPERIDONE OR ARIPIPRAZOLE, RESPECTIVELY WAS ADMINISTERED FOR 1-3 CONSECUTIVE DAYS → ONLY SUBJECTS WHOM **TOLAREATED WELL (SEE NEXT SLIDE) THE ORAL PRODUCT** WERE ENROLLED IN THE STUDY WITH THE LAI**



# MITIGATION MEASURES TAKEN FOR SAFETY RELATED RISKS –CTD.

- **ECG** – several ECGs were performed in the oral product dosing day/s and at 24 and 48 hours after the last oral dose - QT INTERVAL CRITERIA SET
- HEMATOLOGY, BLOOD BIOCHEMISTRY, URINALYSIS
- **Psychiatric examination** (including C-SSRS\*) performed at 48 hours after the last oral dose.
- **Neurological examination and ESRS\*\*** assessment performed at 2 hours post-dose and 26-30 hours after last oral administration
- **THERE WERE 25-30 CRITERIA** FORESEEN IN THE STUDY PROTOCOLS BASED ON WHICH THE INVESTGATOR ASSESSED THE ELIGIBILITY OF EACH SUBJECT FOR THE ENROLMENT IN THE LAI STUDY, AFTER STAGE II OF THE SCREENING WAS COMPLETED
- **\*C-SSRS = Columbia Suicide Severity Rating Scaling**
- **\*\*ESRS = Extrapyramidal Symptom Rating Scale**



## MITIGATION MEASURES TAKEN FOR SAFETY RELATED RISKS – CTD.

- **Confinement at the study Center** – from the evening prior to the LAI administration until the plasma concentrations were in the elimination phase (lower than  $\frac{1}{2}$  C<sub>max</sub>); in practice this meant 3 weeks of continuous confinement for the every 1 month products and 6 weeks of continuous confinement for the every 3 months product
- **Medical supervision 24/24 and 7/7**
- Frequently **scheduled well being and AE check/assessments**
- **Scheduled ECGs** plus the capability to perform ECG at any time, at the slightest sign of cardio-vascular problems
- To avoid postural/orthostatic hypotension **participants were instructed to do not raise sudden from the bed** but to take some few minutes in sitting position prior to standing
- **All meals were served by the participants beds**



# RISKS MITIGATION MEASURES FOR PK RELATED RISKS

## GENERAL:

- **LONG TERM STANDARDIZATION MADE EASY BY THE CONFINEMENT**
- **SAME MEALS WERE SERVED TO ALL SUBJECTS, SAME WATER WAS DRUNK, RESTRICTIONS - ESPECIALLY REGARDING ALCOHOL INTAKE 100% ADHERED TO**
- **CAFFEIN RESTRICTIONS (WHERE APPLICABLE) WERE ALSO 100% ADHERED TO**
- **AVOIDANCE OF STRENUOUS PHYSICAL EXERCISING, etc.**



# RISKS MITIGATION MEASURES FOR PK RELATED RISKS – CTD.



## IN CASE OF LAI AND TRANSDERMAL PATCHES:

- FOR LAI – INJECTION SITE WAS CHOSEN THE SAME FOR ALL SUBJECTS (DELTOID) ON THE COUNTER-LATERAL ARM THAN THE ARM IN WHICH CANNULAS WERE INSERTED FOR PK SAMPLES COLLECTION
- FOR TRANSDERMAL PATCHES: SAME AREAS FOR THE TDS APPLICATION WERE CHOSEN FOR ALL SUBJECTS (E.G. UPPER ARM, ALSO ON THE CONTRALATERAL ARM THAN THE ONE WITH CANNULA FOR PK SAMPLES COLLECTION)

# RISKS MITIGATION MEASURES — DUMPING EFFECT



**SERIOUS SAFETY RISK !**

**POSSIBLE CONSEQUENCES :**

- ❖ Severe sedation, hypotension, extrapyramidal symptoms, or neuroleptic malignant syndrome (rare)
- ❖ ATYPICAL PK PROFILE/S

# RISKS MITIGATION MEASURES – DUMPING EFFECT

**IN CASE OF LAI: WHY CAN HAPPEN ?**

**1. Improper injection technique (e.g., into fat OR A BLOOD VESSEL instead of muscle)**

**MITIGATION: ULTRASOUND CHECK OF THE INJECTION AREA, LONG ENOUGH NEEDLES FOR DEEP INJ**

**2. Defect in formulation**

**MITIGATION: RESCUE MEASURES IN PLACE**

**3. Local tissue reaction altering drug release**

**MITIGATION: RESCUE MEASURES IN PLACE**

# RISKS MITIGATION MEASURES FOR DROP OUT / WITHDRAWAL RELATED RISKS

- THE STAFF INVOLVED IN THE STUDIES CONDUCT, CONSISTENTLY DEMONSTRATED PROFESSIONALISM, EMPATHY, AND RESPECTFUL COMMUNICATION TOWARD ALL PARTICIPANTS
- PARTICIPANTS WERE PROVIDED WITH ACCESS TO THE INTERNET AND TELEVISION, ENSURING CONVENIENT USE FROM THEIR BEDS
- HIGH QUALITY MEDICAL CARE
- THE CONTINUOUS MEDICAL SURVEILLANCE PROVIDED PARTICIPANTS WITH A SUSTAINED SENSE OF SAFETY AND REASSURANCE
- ALL STUDIES WERE COMPLETED WITH A PARTICIPANT WITHDRAWAL RATE OF LESS THAN 10%, CORRESPONDING THUS TO A RETENTION RATE EXCEEDING 90% IN EACH STUDY



# SO WHAT TO DO NOW ? HOW TO BRIDGE THE CLINICAL PRACTICE WITH THE REGULATION ?

- GUIDANCE, GUIDELINES ARE JUST WHAT THEY ARE CALLED GUIDANCES TO BE FOLLOWED BUT **NOT BLINDLY !**
- IN ADDITION TO THE ESTABLISHED GUIDELINES, ALL EU COUNTRIES PROVIDE THE OPPORTUNITY TO REQUEST SCIENTIFIC ADVICE
- IN CASE OF UNCERTAINTY, IT IS A GOOD STRATEGY TO SEEK SCIENTIFIC ADVICE — FROM EMA, OR, IF THIS PROVES TOO COSTLY OR DISPROPORTIONATE TO THE PROJECT, FROM A TRUSTED NATIONAL COMPETENT AUTHORITY WITHIN THE EU
- OR, WHEN EMA SPECIFIC-PRODUCT GUIDANCE DOES NOT EXISTS, LOOK INTO THE US-FDA GUDANCES AND / OR ASK FOR SCIENTIFIC ADVISE BY EMA/ANY EU COUNTRY
- AND IN ADDITION TO THAT: ASSESS WELL THE PROJECT, ASSESS THE RISKS AND THEN PUT IN PLACE VERY GOOD RISKS MITIGATION PLAN/S



# DISCUSSION/CONCLUSIONS

- **NOT ALL RISKS OR MITIGATION MEASURES TAKEN COULD HAVE BEEN PRESENTED HERE, SURELY SOME WERE LEFT OUT BUT THE KEY ONES WERE PRESENTED**
- **THE MOST RISKS WERE CONNECTED TO THE LAI PRODUCTS – LONG ACTING TIME; THEY CANNOT BE REMOVED FROM THE BODY ONCE INJECTED**



# DISCUSSION/CONCLUSIONS

- BESIDE THE ALREADY PRESENTED MEASURES, CARE WAS TAKEN THAT COUNTERACTIVE SPECIFIC MEDICATION FOR EACH MOLECULE UNDER INVESTIGATION WAS PRESENT AT THE CLINICAL SITE IN SUFFICIENT QUANTITY
- TYPE OF **RESCUE MEDICATION PERMITTED OR EVEN RECOMMENDED** IN CASE OF CERTAIN AE (E.G. EXTRAPYRAMIDAL SYNDROM) WAS **DISCUSSED WELL IN ADVANCE FOR EACH STUDY WITH EXPERT IN THE FIELD, EXPERT IN INTESIVE CARE AND EMERGENCY MEDICINE AND CLEARLY PRESENTED IN THE STUDY PROTOCOLS**
- **TRAINING OF THE STAFF INVOLVED** IN EACH STUDY WITH RESPECT TO THE EMERGENCY CARE/MEASURES TO BE TAKEN IN CASE OF SEVERE AND OR SERIOUS AE



# DISCUSSION/CONCLUSIONS

## EXAMPLES OF SPECIFIC RESCUE MEDICATION FORESEEN BY THE STUDY PROTOCOL/S :

- **Acute dystonia:** anticholinergic agent – trihexyphenidyl or diphenhydramine/promethazine
- **Parkinsonism:** low dose of anticholinergic – trihexyphenidyl
- **Akathisia (difficulty sitting still):** beta-blocker propranolol, benzodiazepines – clonazepam and lorazepam, anticholinergic agents – trihexyphenidyl
- **Tardive dyskinesia:** atypical antipsychotics, clozapine, vitamin E
- **Neuroleptic Malignant Syndrome:** skeletal muscle relaxants (dantrolene), benzodiazepine-antispasmodic agents (diazepam, lorazepam), dopamine agonists (bromocriptine, amantadine).



# DISCUSSION/CONCLUSIONS

**OF COURSE ALL THE PREVIOUS WERE EXPECTED AE, SO WHAT ABOUT THE SUSARS ?**

- SUSARS – SUSPECTED UNEXPECTED SERIOUS ADVERS REACTION
- As they are by definition "UNEXPECTED " – is very difficult to totally prevent them **BUT there are some general good measures** which, if taken, **can strongly minimize the risk of SUSARS occurrence:**
  - Exclude participants with high cardiometabolic risks (obesity, uncontrolled diabetes, dyslipidaemia, prolonged QT)
  - Use the lowest strength – **sometime even a fraction of it !**
  - "Sentinel" like approach: small groups in the beginning of a study with a LAI – SGA, then the size of the groups was increased GRADUALLY when no safety concerns were observed/noticed
  - Ongoing monitoring/continuous medical surveillance
  - AS ALREADY WAS SAID, **EXPECT THE UNEXPECTED** AND BE PREPARED



# FEW WORDS ABOUT 3S PHARMACOLOGICAL CONSULTATION & RESEARCH (3S)

- 3S IS A CONTRACT RESEARCH ORGANIZATION WITH 25 + YEARS IN THE FIELD OF CLINICAL RESEARCH
- FOCUSED ON EARLY PHASE CLINICAL STUDIES
- MOST OF THEM HAVING A PK COMPONENT :

BA/BE STUDIES

PK PROFILE

FIRST IN HUMAN

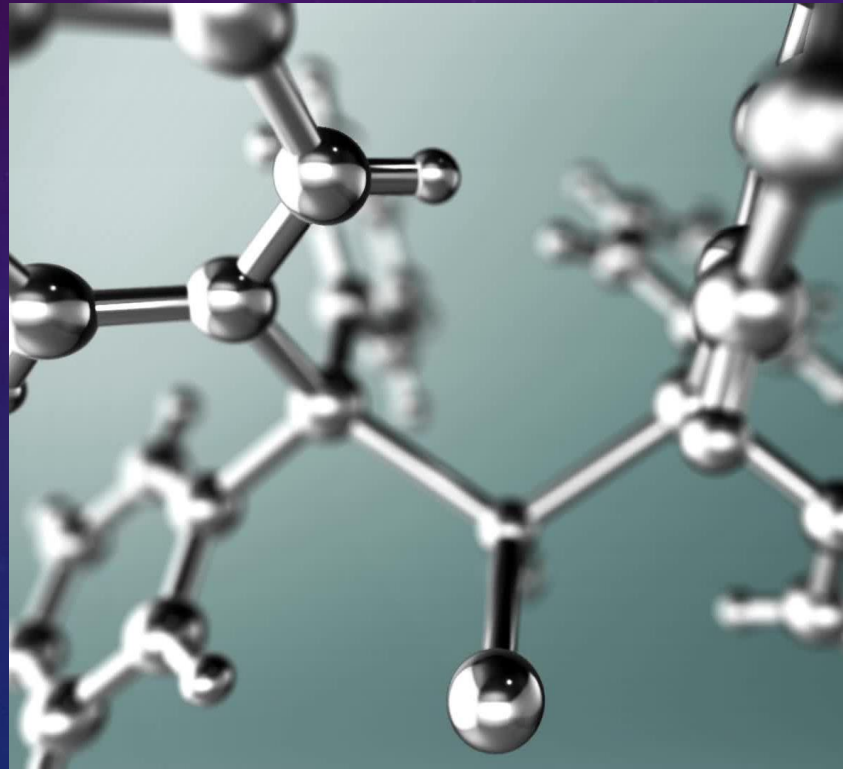
DRUG-DRUG INTERACTION STUDIES

FOOD INTERACTION STUDIES



ALL PERFORMED FOR VARIOUS PHARMACEUTICAL FORMS, BESIDE ORAL FORMS: INJECTABLES (S.C., I.M., I.V.),  
INHALERS, TRANSDERMAL PACTHES AND MORE

THANK YOU VERY MUCH FOR ATTENTION !



**SHOULD YOU REQUIRE ADDITIONAL INFORMATION,  
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