Enablers and Barriers for Regulatory Approval of Schizophrenia Drugs in USA, Canada, UK, and EU

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**Schizophrenia**
- A chronic mental illness that is characterized by psychotic symptoms including hallucinations and delusions.
- Psychotic symptoms are usually categorized as positive symptoms (reflecting a distortion or absence of normal mental activity) and negative symptoms (reflecting a loss or restriction of normal function).

**Objective**
- To compare the factors that favored and hindered the regulatory approvals for marketing and reimbursement of drugs used in the management of all forms of schizophrenia.
- To compare the enablers and barriers in the above-4 regions to identify similarities and differences in the regulatory frameworks in the Schizophrenia space.

**Methodology**

- **Sources of Information**
  - FDA
  - Health Canada
  - Health Canada
  - CADTH
  - MHRA
  - EFPIA
  - EFPIA
  - EFPIA
  - EFPIA

- **Region**
  - USA
  - Canada
  - UK
  - Rest of EU

- **Data Collection**
  - We searched for relevant articles, guidelines, reports, books, and other resources that provided additional insights relevant factors contributing to successful and unsuccessful regulatory decisions by the respective regulatory bodies.

- **Results**
  - **Approved Drugs**
    - | Drug | Route of administration | Sample size | Efficacy measurement | Safety measurement |
    - |-----|-------------------------|-------------|---------------------|-------------------|
    - | Olanzapine + Samidorphan (Oral) | - | 306 | PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity) | Prolactin elevation and neuroleptic malignant syndrome |
    - | Brexpiprazole (Oral) | - | 24 | PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity) | Prolactin elevation and neuroleptic malignant syndrome |
    - | Cariprazine (Oral) | - | 320 | PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity) | Prolactin elevation and neuroleptic malignant syndrome |
    - | Paliperidone palmitate (IM) | - | 1065 | PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity) | Prolactin elevation and neuroleptic malignant syndrome |
    - | Aripiprazole (IM) | - | 1262 | PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity) | Prolactin elevation and neuroleptic malignant syndrome |
    - | Lurasidone (Oral) | - | 702 | PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity) | Prolactin elevation and neuroleptic malignant syndrome |

- **Study Design**
  - **Clinical outcomes**
    - **Efficacy**
      - Time to relapse, % relapsed
    - **Safety**
      - Prolactin elevation and neuroleptic malignant syndrome
  - **Study duration**
    - Long enough to establish efficacy
  - **Randomization and blinding**
    - Active comparator; placebo was also used in a 4 arm trial
  - **Enrollment criteria**
    - BMI between 18 to 35
  - **Measuring relapse**
    - Time to relapse, % relapsed
  - **Key efficacy scales used**
    - PANSS (positive and negative syndrome scale), CGI-S (clinical global impression-severity)

- **Barriers**
  - **Economic outcomes**
    - Limited healthcare access (PP3M, risperidone, aripiprazole)
    - Weight gain, extrapyramidal symptoms, prolactin elevation, limited healthcare access (PP3M)
    - Extra-pyramidal symptoms (lurasidone, aripiprazole, brexipiprazole)
    - Insomnia (aripiprazole)
  - **Safety**
    - Prolactin elevation and neuroleptic malignant syndrome
  - **Regulatory**
    - USFDA raised some concerns during the course of regulatory review
  - **Regulatory pathways**
    - Although we could not find any regulatory rejections by USFDA during the period of interest for schizophrenia, the USFDA raised some concerns during the course of regulatory review

- **Conclusions**
  - **Product development**
    - This can improve the methodology of ethical & scientific evidence generation, and can ultimately facilitate earlier market access of drugs for Schizophrenia

**References**


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