Multicenter observational program

TELESPHOR

Protocol №:IC4-20098-069-RUS

NCT05323994

DescripTion of the Effectiveness and tolerability of agomeLatine in the trEatment of patientS with dePression occurred after tHe COVID 19 infectiOn in the daily clinical practice in Russia

02/02/2022

Objectives

Primary objective

- To describe the antidepressive effectiveness of agomelatine in patients with depression episode occurred after COVID-19 assessed by HAMD-17 after 8 weeks of treatment in the daily clinical practice.

Secondary objectives

- To describe effectiveness of agomelatine on anxiety symptoms assotiated with the depression and assessed by HAMD-17 (point 10 and 11) after 8 weeks of treatment of patients included in the study.
- To describe effectiveness of agomelatine on global improvement and social functioning assessed by CGI score after 8 weeks of treatment of patients included in the study.
- To describe effectiveness of agomelatine on quality of life in patients with depression episode occurred after COVID-19 assessed by SF-36 questionnaire after 8 weeks of treatment of patients included in the study.
- To describe tolerability of agomelatine after 8 weeks of treatment based on rate of adverse events leading to drug discontinuation in patients included in the study.

Study variables

Primary variables:

- Mean change from baseline (BL) in total HAMD-17 score assessed at week 8 of the observational period.

Secondary variables:

- % of patients defined as responders to the treatment (HAMD-17 total score decrease ≥ 50%) at week 8 of the observational period.
- % of patients achieving disease remission (defined as HAMD-17 total score < 7) at week 8 of the observational period.
- Mean change from BL in HAMD-17 point 10 “psychological anxiety” assessed at week 8 of the observational period.
- Mean change from BL in HAMD-17 point 11 “somatic anxiety”assessed at week 8 of the observational period.
- Mean change in scores of the Clinical Global Impression scale (CGI), item 2 (global improvement) at W2,W4,W8 assessed at week 8 of the observational period.
- Mean change from BL in total score of the SF-36 QoL questionnaire reported by patients at week 8 of the observational period.
- Mean change from BL in score of the SF-36 QoL questionnaire (physical component) reported by patients at week 8 of the observational period.
- Mean change from BL in score of the SF-36 QoL questionnaire (psychiatric component) reported by patients at week 8 of the observational period.

- Number of adverse events/ adverse drug reactions leading to drug discontinuation during the observational period.

Methods and documentation

Study design and methodology

This is a multi-centre, observational, non-interventional study, which will prospectively collect clinical and socio-demographic data from patients with depression occurred after COVID 19 in real clinical settings during 8 weeks of treatment.

At Visit 0 (V0), investigating psychiatrist or neurologist will evaluate patient's eligibility for the study according to inclusion/non-inclusion criteria. Only patients who comply with all inclusion/ non inclusion creteria will be invited to participate in this observational study. Recommendation to start treatment with agomelatine to manage depressive episode is to be done by investigating psychiatrist/ neurologist before and independently from the decision to invite a patient to participate in the study. Agomelatine should be administered to patients in accordance to the instruction for medical use approved in the Russian Federation (RF).

20 clinics and 20 of psychiatrists and neurologists across the country will participate in the study and it is estimated that each investigating physician will enroll at least 5 of patients.

Once a patient will provide his/her consent to participate in the study, investigating physician will record information from appointments for the evaluation of treatment in a routine clinical practice. The frequency of the appointments reflects a routine clinical practice of management of outpatients with depressive disorders in the RF.

Main millestones:

Local Ethic Committee approval – 1q22

First patient included – March 2022

Last patient included – July 2022

End of treatment period – September 2022

Clinical statistic subdevelopment – August 2022

Data based lock – October 2022

Clinical statistic subdevelopment report – November-December 2022

End of clinical study – February 2023

Selection of the study population

Inclusion criteria

1. Obtained signed informed consent from the patient.
2. Age of 18-65 years old.

3. Out-patient with confirmed COVID 19 infection within 3 months period before the date of inclusion.
4. Confirmed depression with total HAMD-17 score of 8-24 required treatment with antidepressive medicines.
5. Decision to administer agomelatine preceeds the decision to include a patient in the study.

Non-inclusion criteria

1. Current participation in any clinical trial or during 30 day period from inclusion visit.
2. Suicide risk (accoding clinical evaluation of investigator).
3. Psychotics symptoms (according clinical evaluation of investigator).
4. Schizophrenia, schizo-affective disorders, organic damages of CNS, dementia, epilepsy, multiple sclerosis, Parkinson disease, Alzeimert disease, Bipolar disorders.
5. Alcohol abuse or drug addiction in anamnesis.
6. Severe or decompensated somatic or neurological disorders.
7. MAO inhibitors during last 2 weeks.
8. Treatment by others psychotropic products (antipsychotics, anxiolitics etc.).
9. Any contraindications to agomelatine in accordance to the local SmPC.

Exclusion criteria

1. Patients with severe/decompensated psychiatric, somatic or neurological disorders.
2. Patients with any sign of liver failure (increase of transaminase up to 3 times higher), which needs to stop treatment with agomelatine.
3. Patients who participate in any clinical trial or survey.

Therapeutic strategy during the study The assignment of a subject to a particular therapeutic strategy is not supposed by this protocol due to the observational nature of the study. Treatment approaches to depressed patients are based on local clinical recommendations and clinical experience of HCPs. Decision on agomelatine administration must be made with accordance to established SmPC, local standards and guidelines and must be independent from and proceeding the decision of the physician to include a patient in this study.

Study plan and procedures

A patient with depression occurred within 3 month period after onset of confirmed COVID 19 infection who has already been recommended to initiate antidepressive treatment with agomelatine will be asked to provide a consent to participate in the study and in case of consent is positive the patient will be invited for 3 more visits starting from the date of the inclusion in the study according to clinical practice. Therefore clinical parameters needed for describing effectiveness and tolerability of agomelatine treatment will be prospectively collected at each of these visits.

Antidepressive treatment of enrolled outpatients can be modified by investigating psychiatrist or neurologist at any time of the observation if required.

Following visits are planned:

1. Inclusion Visit 0 (V0) – inclusion in the study

2. Follow up Visits 1-2 (V1-V2) – visits at week 2 and week 4 after V0.

3. Final Visit 3 (V3) – visit at week 8 after V0.

Table 1 – Planned study visits and collecting parameters at each visit

Procedure	**Inclusion Visit 0**	**Visit 1 at W2**	**Visit 2 at W4**	**Visit 3 at W8**
Written informed consent	**X**			
Assessment in accordance to inclusion/ non-inclusion criteria	**X**			
Assessment in accordance to exclusion criteria		**X**	**X**	**X**
Demographics	**X**			
HAMD-17	**X**	**X**	**X**	**X**
CGI -I		**X**	**X**	**X**
SF-36	**X**	**X**	**X**	**X**
Current treatment with other concomitant medications	**X**	**X**	**X**	**X**
Adverse events/drug reactions/ special situations reporting		**X**	**X**	**X**

Data evaluation/collection at the incusion visit (V0):

HCPs participating in the study will prospectively evaluate patient's eligibility to be enrolled in the study. Following data will be prospectively collected at the inclusion visit:

- Obtained patient's consent.
- Meeting to inclusion/non-inclusion criteria.
- Demographics.
- Confirmation of COVID 19 infection within 3 month period.
- HAMD-17 score.
- Concomitant current use of other medications.
- Quality of life assessment (SF-36).

Data collection at the Follow up Visit (V1 – week 2):

- HAMD-17 score.

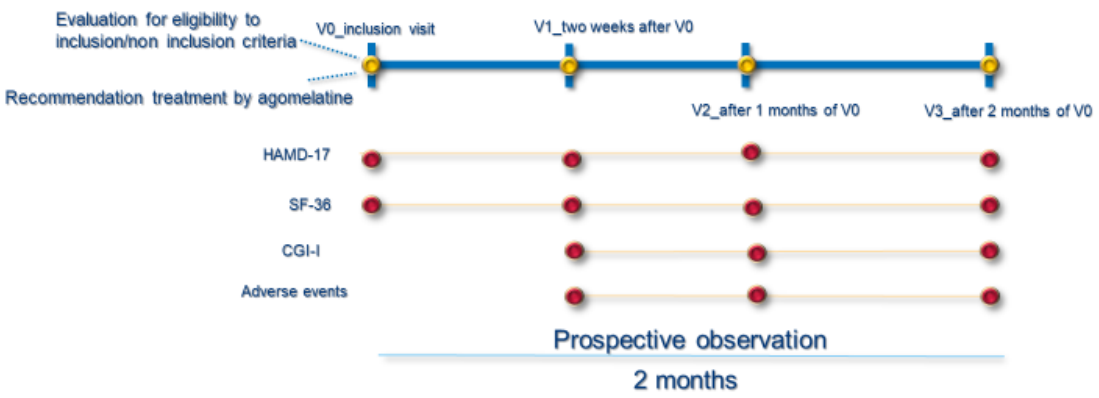
- CGI-Improvement score.
- Presence of exclusion criteria.
- Concomitant current use of other medications.
- Quality of life assessment (SF-36).
- Adverse events/drug reactions/special situations.
- Change in therapy with agomelatine if occurred or required.

Data collection at the Follow up Visit (V2 - week 4):

- HAMD-17 score.
- CGI-Improvement score.
- Presence of exclusion criteria.
- Concomitant current use of other medications.
- Quality of life assessment (SF-36).
- Adverse events/drug reactions/special situations.
- Change in therapy with agomelatine if occurred or required.

Data collection at the Final Visit (V3 - week 8):

- HAMD-17 score.
- CGI-Improvement score.
- Presence of exclusion criteria.
- Concomitant current use of other medications.
- Quality of life assessment (SF-36).
- Adverse events/drug reactions/special situations.
- Change in therapy with agomelatine if occurred or required.



Statistical analysis

Due to non-interventional nature of the study design descriptive statistical methods will be used. Search statistical analysis will be performed in the following groups of patients: in the clinical study the primary end point of the study is a mean change from BL in HAMD-17 total score assessed at week 8 of the observational period.

In the article of O.V. Vorob'eva "Valdoxan in the Treatment of Depression in Neurological Practice: Results of the Russian Multicenter Naturalistic Study "Resonance" from Zhurnal Nevrologii i Psikhiatrii imeni S. S. Korsakova, Vol. 112, No. 9, Iss. I, pp. 47—51, September, 2012, was described the efficacy and tolerance of Valdoxan (agomelatine) in mild and moderate depression due to neurological diseases. Treatment efficacy was evaluated using standard psychometric tools, one of them was the 17-point Hamilton depression scale (HAMD-17).

The mean total score on the HAMD-17 was 15.3 ± 3.8 points. Significant decreases in total points scores on the HAMD-17 were seen by the end of the first week of treatment. After completion of treatment courses (at six weeks of treatment), the mean score was 4.7 ± 3.2 points. At six weeks of treatment, responders (patients with total HAMD-17 scores which decreased at least twofold) constituted 82.33% of all patients treated.

The following general assumptions were made for the sample size calculations:

1) One-sided (directional) statistical hypothesis for mean:

   $H0: m1 - m0 \leq 0$

   $HA: m1 - m0 > 0$

where m1 stands for sample (study) mean of the corresponding variable (change from BL in HADS total score assessed at week 8 of the observational period), and m0 stands for the population mean (constant).

2) Possible standard deviation is 3.8 points

3) Planned study power is 90%, accordingly, type II (β) error is 0.1

4) Overall significance level is 0.01 that corresponds to two-sided type I (α) error of 0.01 or one-sided type I (α) error of 0.005

5) Dropout during the study period to 30%.

Calculations for each of the parameters listed above were performed using the validated PASS sample size calculation software, with main outputs (screenshots) provided under the assumptions summarized above.

One-Sample T-Tests

Numeric Results

Hypotheses: H0: μ ≤ μ0 vs. H1: μ > μ0

Power	N	μ0	μ1	Diff μ1 - μ0	σ	Effect Size	Alpha	Beta
		0	0,0	0,0	3,8	0,00000	0,005	
0,90031	861	0	0,5	0,5	3,8	0,13158	0,005	0,09969
0,90127	219	0	1,0	1,0	3,8	0,26316	0,005	0,09873
0,90059	99	0	1,5	1,5	3,8	0,39474	0,005	0,09941
0,90571	58	0	2,0	2,0	3,8	0,52632	0,005	0,09429
0,90242	38	0	2,5	2,5	3,8	0,65789	0,005	0,09758
0,90991	28	0	3,0	3,0	3,8	0,78947	0,005	0,09009
0,90091	21	0	3,5	3,5	3,8	0,92105	0,005	0,09909
0,90346	17	0	4,0	4,0	3,8	1,05263	0,005	0,09654

References

Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

Machin, D., Campbell, M., Fayers, P., and Pinol, A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, MA.

Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.

As can be seen from the various scenarios provided depending on the planned difference, approximately 28 study subjects will be enough to detect at least a 3.0-point difference between the sample and population means with 90% power at 0.005 one-sided significance level. Dropout-Inflated Enrollment Sample Size is 40 study subjects.

Despite that sample size calculation is 40 patients, at least 100 patients with MDD will be invited to participate in the study.

Safety

Definitions

Pharmacovigilance information

Pharmacovigilance data include any unintended or adverse event associated with the use of a medicinal product in humans, whether or not considered drug related, including the following special situations (situations where no adverse event occurred but information needs to be collected):

- exposure during pregnancy or breastfeeding;
- overdose, abuse, misuse, off-label uses, medication error, occupational exposure (including professional one);
- lack of efficacy.
- any suspected transmission via a medicinal product of an infectious agent,
- unintended therapeutic benefit.

Adverse event (AE)

Adverse event (AE) is any untoward medical occurrence in a patient or clinical-trial participant administered the medicinal product, which does not necessarily have a causal relationship with the use of this medicinal product.

An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered as related to the medicinal product.

Adverse (drug) reaction (ADR)

Adverse reaction (synonyms: Adverse drug reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect) is a response to a medicinal product which is noxious and unintended.

Response" in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse (drug) reaction (SADR)

Serious adverse reaction is an adverse reaction, which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death in case of more severe course.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered as serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered as a serious adverse reaction.

Responsibilities

- Events to be reported
- All available information about the following events reported during the study will be recorded:

All serious adverse drug reactions related to the use of Agomelatine

- All non-serious adverse drug reactions related to the use of Agomelatine
- All reports about special situations (see section Pharmacovigilance information)

- All adverse events

Specific attention should be paid to increase of ALT and/or AST, ALP value >3 ULN and increase of total bilirubin > 2 ULN.

Responsibilities of investigator

In prospective studies, at medical visits the investigator will ask a participating patient to indicate whether or not an adverse event (serious or not) has occurred.

Investigator has to assess causal relationship between an adverse event and the investigated drug intake, as well as the seriousness criteria and later on the outcome of the event.

In case of Adverse Events, Adverse Drug Reactions or special situations that occurs during the study (both serious and non-serious), the investigator must complete the "Adverse event / Adverse drug reaction / Special Situation Reporting Form" (Appendix 4) without waiting for the clinical outcome or the results of additional investigations.

If the event is serious, it will be notified immediately (same or next working day at the latest) to Servier company in Russia via e-mail to address pvmail.rus@servier.com or by fax to number (495) 937-47-66. The anonymized copies of all the available and relevant laboratory findings, hospitalisation reports or other investigation results performed in connection with the adverse event should be attached to the form.

All other events should be reported by investigator within 2 working days.

The same rules apply for the transferring of additional information about the event.

The investigator must ensure the appropriate follow-up of the patient depending on the nature of event, until it resolves. The investigator will continue to notify follow up data according to timeframes defined above.

If investigator does not follow-up a patients anymore (i.e. in case of hospitalization followed by the treatment by specialist or the participant's general practitioner,…), he/she will do every effort to contact the specialist or department in charge of follow-up of the patient, so as to have additional information and report it to Servier company in Russia.

Responsibilities of sponsor/marketing authorization holder (MAH)

Independently of the regulatory obligations of investigator, the sponsor/MAH must report the pharmacovigilance data to the appropriate authorities in accordance with the Good Vigilance Practice and local regulations.

Cases are closed when an adverse event has recovered or patient's condition was stabilized and the report is deemed sufficiently detailed for adequate medical analysis of the case.

Data Management

- Data collection in this study is carried out using documentation forms. Centralized data entry will be performed by the responsible professional subcontractor for statistical analyses after receiving the documentation forms. The statistical analysis of the data and the creation of the final statistical report on the study will also be carried out by a responsible professional subcontractor for statistical analyses.
- Discrepancies will be resolved by mutual agreement between both parties (Servier and professional subcontractor for statistical analysis).

Biometrics

- Due to the non-interventional nature of this study, statistical analysis will be conducted in a descriptive and searchable form. All indicators will be analyzed using descriptive statistics methods. For each indicator, the number of patients, the average value, the standard error, the minimum and maximum values, or the proportion of each category will be specified. All composite indicators will be
- listed and presented in visual form as graphs and frequency distribution tables / indicator tables.
- Absolute and percentage frequencies will be calculated for categorical variables. Only patients for whom data on the corresponding variables will be available will be included in the relative frequency calculations.
- All reports of adverse drug reactions, adverse events, and special situations will be coded using MedDRA, and the results will be listed and classified according to classes for organ and organ systems (system-Organ-Class; SOC) by the statisticial agency during preparation of final report.

Publications and communication

- The sponsor is responsible for communicating and publishing research data. No part of the results of this study or other data may be published, presented or distributed without the express written permission of Sponsor. Participants in the study fully transfer to the Sponsor the authority for the first presentation, communication and publication of the results on behalf of all employees. No other communication or publication is permitted before this first publication. Any subsequent communication or publication must first be reviewed and approved by the Sponsor and should refer to the research and the first publication.

Ethic aspects

- The study will be conducted in accordance with the principles of the Helsinki Declaration, according to the version revised in Brazil in 2013.
- The Protocol must be reviewed and approved by an independent ethics Committee after being submitted by the coordinator or sponsor in accordance with local regulatory requirements, especially with regard to data protection.

Confidentiality of patient data

- Researchers are required to maintain the confidentiality of information about patients included in this study. Confidential data should contain enough information to contact the patient in case of an emergency, or if further monitoring is required.

To protect data privacy and keep patients anonymous, their identity will be encoded in the research documentation. Patients can be identified using a unique number that will be recorded and the CRF. In order to reveal the patient's identity, all researchers will have a confidential list of patient identification containing the names and phone numbers. Thus, only the researcher will be able to decode the patient's identity.

Appendix 1.

THE HAMILTON RATING SCALE FOR DEPRESSION (HAMD-17)

Instructions.

For assessment please choose one answer that best characterizes the patient's condition.

For item 7 (work and activities) the researcher can obtain information from relatives or medical personnel.

Item 16 (weight loss) requires an answer only by one of the proposed points 16A and 16B according to the "yes or no". The assessment of body weight changes is more preferable during therapy (16B). The assessment of weight change on anamnestic information (16A) is used only as initial, before starting therapy.

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1 **DEPRESSED MOOD**

(sadness, hopeless, helpless, worthless)

0- Absent

1- These feeling states indicated only on questioning

2- These feeling states spontaneously reported verbally

3- Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep

4- Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication

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2 **FEELINGS OF GUILT**

0- Absent

1- Self-reproach, feels he has let people down

2- Ideas of guilt or rumination over past errors or sinful deeds

3- Present illness is a punishment. Delusions of guilt

4- Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

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3 **SUICIDE**

0 - Absent

1 - Feels life is not worth living
2 - Wishes he were dead or any thoughts of possible death to self
3 - Suicidal ideas or gesture
4 - Attempts at suicide (any serious attempt rates 4)

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4 **INSOMNIA EARLY**

0- No difficulty falling asleep

1- Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour

2- Complains of nightly difficulty falling asleep

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5 **INSOMNIA MIDDLE**

0- No difficulty

1- Patient complains of being restless and disturbed during the night

2- Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

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6 **INSOMNIA LATE**

0- No difficulty

1- Waking in early hours of the morning but goes back to sleep

2- Unable to fall asleep again if he gets out of bed

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7 **WORK AND ACTIVITIES**

0- No difficulty

1- Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies

2- Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)

3- Decrease in actual time spent in activities or decrease in productivity. In hospital settings the mark “3” is stated if patient’s activity is exhibited during at least 3 hours per day (working in a hospital or a hobby)

4- Stopped working because of present illness.

In hospital settings the mark “4” is stated if patient does not exhibit activity or does not cope even with routine household activity without assistance.

8 **RETARDATION: PSYCHOMOTOR**

(slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

0- Normal speech and thought

1- Slight retardation at interview

2- Obvious retardation at interview

3- Interview difficult

4- Complete stupor

9 **AGITATION**

0- None

1- Fidgetiness

2- Playing with hands, hair, etc.

3- Moving about, can't sit still

4- Hand wringing, nail biting, hair-pulling, biting of lips

10 **ANXIETY (PSYCHOLOGICAL)**

0- No difficulty

1- Subjective tension and irritability

2- Worrying about minor matters

3- Apprehensive attitude apparent in face or speech

4- Fears expressed without questioning

11 **ANXIETY SOMATIC**

(Physiological concomitants of anxiety: **gastrointestinal** - dry mouth, "butterflies," indigestion, stomach cramps, belching, diarrhea;

cardiovascular – palpitations, headache; **respiratory** – hyperventilation, dyspnea; **urinary frequency; sweating**)

0- Absent

1- Mild

2- Moderate

3- Severe

4- Incapacitating

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12 **SOMATIC SYMPTOMS (GASTROINTESTINAL)**

0- None

1- Loss of appetite but eating without encouragement from others. Food intake about normal

2- Difficulty eating without urging from others. Requirement in laxatives and drugs for relief of gastrointestinal symptoms

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13 **SOMATIC SYMPTOMS GENERAL**

0- None

1- Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability

2- Any clear-cut symptom rates

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14 **GENITAL SYMPTOMS**

0- Absent

1- Mild – loss of libido

2- Severe – menstrual disturbances

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15 **HYPOCHONDRIASIS**

0- Not present

1- Self-absorption (bodily)

2- Preoccupation with health

3- Frequent complaints, requests for help, etc.

4- Hypochondriacal delusions

LOSS OF WEIGHT (either A or B is used)

16A

A. When rating by history:

0- No weight loss

1- Probably weight loss associated with present illness

16B 2- Definite (according to patient) weight loss

3- Not assessed

B. If loss of weight is observed each week and is actual now

0- Less than 0.5 kg per week

1- More than 0.5 kg per week

2- more than 1 kg per week

3- Not assessed

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17 **INSIGHT**

0- Acknowledges being depressed and ill

1- Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.

2- Denies being ill at all

Table for recording scores by Hamilton Depression Rating Scale

Total score by HAMD-17 scale:_____

Assessment of the severity of condition using Hamilton Depression Rating Scale:

0 – 7 «normal» (no marked symptoms of anxiety and depression)

8 – 15 «mild depression»

16 – 24 «moderate depression»

25 and more «severe depression»

.

Appendix 2.

Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36)

About: The SF-36 is an indicator of overall health status.

Items: 10

Reliability: Most of these studies that examined the reliability of the SF_36 have exceeded 0.80 (McHorney et al., 1994; Ware et al., 1993). Estimates of reliability in the physical and mental sections are typically above 0.90.

Validity: The SF-36 is also well validated.

Scoring:
The SF-36 has eight scaled scores; the scores are weighted sums of the questions in each section. Scores range from 0 - 100
Lower scores = more disability, higher scores = less disability
Sections:

- Vitality
- Physical functioning
- Bodily pain
- General health perceptions
- Physical role functioning
- Emotional role functioning
- Social role functioning
- Mental health

References:

McHorney CA, Ware JE, Lu JFR, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36®): III. tests of data quality, scaling assumptions and reliability across diverse patient groups. *Med Care*1994; 32(4):40-66.

Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36® Health Survey Manual and Interpretation Guide*. Boston, MA: New England Medical Center, The Health Institute, 1993.

Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36®): I. conceptual framework and item selection. Med Care 1992; 30(6):473-83.

Medical Outcomes Study Questionnaire Short Form 36 Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please circle the number that best describes your answer.

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5
2. Compared to one year ago,	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
(Circle One Number on Each Line)

	Yes, Limited a Lot (1)	**Yes, Limited a Little (2)**	**No, Not limited at All (3)**
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3

g. Walking **more than a mile**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?
(Circle One Number on Each Line)

	Yes (1)	**No (2)**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(Circle One Number on Each Line)

	Yes	**No**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks?	
None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. **(Circle One Number on Each Line)**

9. How much of the time during the **past 4 weeks** . . .

	All of the Time	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (Circle One Number)	
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements for you. (Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Appendix 3.

At ASSE and W0 visits, the global improvement (CGI-I) is not assessed.

Cross the appropriate box.

1. Severity of illness Considering your total experience with this particular population, how ill is the patient at this time?		**2. Global improvement** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment. Compared to his condition at **the inclusion visit** how much has he changed?	
☐ **0**	Not assessed	☐ **0**	Not assessed
☐ **1**	Normal, not at all ill	☐ **1**	Very much improved
☐ **2**	Borderline mentally ill	☐ **2**	Much improved
☐ **3**	Mildly ill	☐ **3**	Minimally improved
☐ **4**	Moderately ill	☐ **4**	No change
☐ **5**	Markedly ill	☐ **5**	Minimally worse
☐ **6**	Severely ill	☐ **6**	Much worse
☐ **7**	Among the most extremely ill patients	☐ **7**	Very much worse

Appendix 4 Form for reporting an adverse event / adverse drug reaction / special situations

IC4-20098-069- RUS *Please send this form immediately by fax (495) 937-47-66 or by email to pvmail.rus@servier.com, or pass to the associate of the company.*

Year of birth or Age	**Gender**	**Height**	**Weight**	**Patient's ID:**
|__|__|__|__| or |__|__|__|	M / F	|__|__|__|	|__|__|__|	|_|_|_|_|_|_|_|_|_|_|

Description of adverse event/reaction/special situation:	**Date of event onset** |_|_| |_|_| |_|_|_|_|	**Date of event termination (in case of recovery)** |_|_| |_|_| |_|_|_|_|

Criteria of seriousness: ☐ NO ☐ YES (please, specify from stated below) ☐ Death ☐ Life threatening ☐ Hospitalization or prolongation of existing hospitalisation ☐ Persistent or significant disability or incapacity ☐ Congenital anomaly/birth defect ☐ Medically significant	**Outcome:** ☐ Recovered ☐ Recovered with consequences (persistent structural or functional impairment) ☐ Not recovered ☐ No recovered ☐ Death ☐ Unknown

General disease(s) / Concomitant disease(s) (please indicate year when first diagnosed).

Course adverse event/reaction/special situation (please enclose relevant findings, e.g. laboratory, hospital reports, histology, etc.):

Causal relationship with intake of <u>studied</u> drug:
☐ NO ☐ YES ☐ NOT APPLICABLE

***If «Yes»**, please indicate dates of the use of studied drug <u>in the first line</u> of the table below:*

***If «No» or «Not applicable»**, please specify whether the adverse event/special situation is related to the medication of Servier company (which is specified in the table below)*:
☐ NO ☐ YES *Please indicate the name of the medication of Servier company*: ……

List of current medications	**Daily dose / route of administration**	**Dates of intake: from to**	**Indication**
		-	
		-	
		-	

Name (last, first, patronymic) of doctor: Speciality: Work address: Phone number: _____ (city code)	Date: Stamp Signature: (whenever possible)

**Special situations are cases when adverse event was not observed, but the information should be collected: the impact of the drug during pregnancy/breastfeeding, abuse, misuse, medication error, overdose, off-label use, occupational exposure, or lack of efficacy*, any suspected transmission via medicinal product of an infection agent, unintended therapeutic benefit…