

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203479Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY ADDENDUM TO THE NDA REVIEW DATED
OCTOBER 9, 2012**

Application number: 203479
Supporting document/s: SDN 1; Sequence No. 0000
Applicant's letter date: December 28, 2011
CDER stamp date: January 6, 2012
Product: Versacloz (clozapine oral suspension) 50
mg/mL
Indication: Treatment resistant schizophrenia and to reduce
the risk of recurrent suicidal behavior in patients
with schizophrenia and schizoaffective disorder
Applicant: Douglas Pharmaceuticals America LTD
Review Division: DPP
Reviewer: Elzbieta Chalecka-Franaszek, Ph.D.
Supervisor/Team Leader: Aisar Atrakchi, Ph.D.
Division Director: Thomas Laughren, M.D.
Project Manager: Sharonjit Sagoo, Pharm. D.

LABELING ADDENDUM

The following text is proposed for sections 8.1, 12.1, 12.2 and 13.1 of the clozapine label.

Labeling changes for sections 8.1 and 13.1 are based on the summary of nonclinical studies conducted with clozapine as described in the Summary Basis of Approval dated September 26, 1989.

Labeling changes for sections 12.1 and 12.2 are based on the NIMH Psychoactive Drug Screening Program K_i Database. The data are averaged K_i values (nM) from published sources determined by competition with radioligands for binding to the indicated cloned human receptors. Data derived from receptor binding to human or rat brain tissue is used when cloned human receptor data is lacking. Affinities of clozapine for selected receptors (5-HT₃, 5-HT₆, 5-HT₇, D₃ and D₄) are adopted from published literature (H. Y. Meltzer, An Overview of the Mechanism of Action of Clozapine, J. Clin. Psychiatry, 55:9, 1994).

Note: new text is underlined.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate or well-controlled studies of clozapine in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 0.4 and 0.9 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis and have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Clinical Considerations

Consider the risk of exacerbation of psychosis when discontinuing or changing treatment with antipsychotic medications during pregnancy and postpartum. Consider early screening for gestational diabetes for patients on antipsychotic medications. [see 5.X Metabolic Adverse Reactions]

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Monitor neonates for symptoms of agitation, hypertonia, hypotonia, tremor, somnolence,

respiratory distress, and feeding difficulties. The severity of complications can vary from self-limited symptoms to some neonates requiring intensive care unit support and prolonged hospitalization.

Human Data

Animal Data

In embryofetal developmental studies, clozapine had no effects on maternal parameters, litter sizes or fetal parameters when administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 0.4 and 0.9 times, respectively, the MRHD of 900 mg/day on a mg/m^2 body surface area basis.

In peri/postnatal developmental studies, pregnant female rats were administered clozapine over the last third of pregnancy and until day 21 postpartum. Observations were made on fetuses at birth and during the postnatal period; the offspring were allowed to reach sexual maturity and mated. Clozapine caused a decrease in maternal body weight but had no effects on litter size or body weights of either F1 or F2 generations at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m^2 body surface area basis.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of clozapine is unknown. However, it has been proposed that the therapeutic efficacy of clozapine in schizophrenia is mediated through antagonism of the dopamine type 2 (D_2) and the serotonin type 2A (5-HT_{2A}) receptors. Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and other dopaminergic and serotonergic receptors, which may explain some additional effects of the drug.

12.2 Pharmacodynamics

Clozapine showed binding affinity to the following receptors: histamine H_1 (K_i 1.1 nM), adrenergic α_{1A} (K_i 1.6 nM), serotonin 5-HT_6 (K_i 4 nM), serotonin 5-HT_{2A} (K_i 5.4 nM), muscarinic M_1 (K_i 6.2 nM), serotonin 5-HT_7 (K_i 6.3 nM), serotonin 5-HT_{2C} (K_i 9.4 nM), dopamine D_4 (K_i 24 nM), adrenergic α_{2A} (K_i 90 nM), serotonin 5HT_3 (K_i 95 nM), serotonin 5-HT_{1A} (K_i 120 nM), dopamine D_2 (K_i 160 nM), dopamine D_1 (K_i 270 nM), dopamine D_5 (K_i 454 nM), and dopamine D_3 (K_i 555 nM).

FAZACLO causes little or no prolactin elevation.

Clinical electroencephalogram (EEG) studies demonstrated that clozapine increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs. Sharp wave activity and spike and wave complexes may also

develop. Patients have reported an intensification of dream activity during clozapine therapy. REM sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

3 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses up to 0.3 times and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis.

Mutagenesis

Clozapine was not genotoxic when tested in the following gene mutation and chromosomal aberration tests: the bacterial Ames test, the *in vitro* mammalian V79 in Chinese hamster cells, the *in vitro* unscheduled DNA synthesis in rat hepatocytes or the *in vivo* micronucleus assay in mice.

Impairment of Fertility

Clozapine had no effect on any parameters of fertility, pregnancy, fetal weight or postnatal development when administered orally to male rats 70 days before mating and to female rats for 14 days before mating at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m² body surface area basis.

Elzbieta Chalecka-Franaszek, Ph.D., Pharmacologist {see appended electronic signature page}

Aisar Atrakchi, Ph.D., Supervisor {see appended electronic signature page}

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELZBIETA CHALECKA FRANASZ
10/18/2012

AISAR H ATRAKCHI
10/19/2012

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 203479
Supporting document/s: SDN 1; Sequence No. 0000
Applicant's letter date: December 28, 2011
CDER stamp date: January 6, 2012
Product: Versacloz (clozapine oral suspension) 50 mg/mL
Indication: Treatment resistant schizophrenia and to reduce the risk of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder
Applicant: Douglas Pharmaceuticals America LTD
Review Division: DPP
Reviewer: Elzbieta Chalecka-Franaszek, Ph.D.
Supervisor/Team Leader: Aisar Atrakchi, Ph.D.
Division Director: Thomas Laughren, M.D.
Project Manager: Sharonjit Sagoo, Pharm. D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203479 are owned by Douglas Pharmaceuticals America LTD or are data for which Douglas Pharmaceuticals America LTD has obtained a written right of reference. Any information or data necessary for approval of NDA 203479 that Douglas Pharmaceuticals America LTD does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203479.

1 Executive Summary

1.1 Introduction

Clozapine is an atypical antipsychotic marketed in the U.S. as Clozaril® and generic tablets in strengths of 12.5 mg, 25 mg, 50 mg, 100 mg, and 200 mg, and as FazaClo® orally disintegrating tablets in strengths of 12.5 mg, 25 mg, 100 mg, 150 mg, and 200 mg. It is approved for the management of treatment resistant schizophrenia and to reduce the risk of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder. Due to known risk of agranulocytosis associated with clozapine treatment, all clozapine products in the U.S. are distributed under controlled systems which require patient registration and frequent monitoring of white blood cell and absolute neutrophil counts in order for patients to receive clozapine.

Douglas Pharmaceuticals America LTD (the Sponsor) submitted a 505(b) (2) NDA application for clozapine oral suspension, 50 mg/mL, which relies on the Agency's previous finding of safety and efficacy of the listed drug Clozaril® (Clozapine Tablets), NDA 19758. The 505(b)(2) NDA provides for a change in dosage form (i.e., from an oral tablet to an oral suspension).

There are currently no liquid/suspension dosage forms of clozapine in the U.S. The Sponsor believes the proposed product will meet an unmet medical need by providing a suspension formulation for those patients with swallowing difficulty or patients who "cheek" their medication.

1.2 Brief Discussion of Nonclinical Findings

No additional nonclinical safety data were required for this NDA as indicated in the IND 108466 Meeting Minutes dated July 20, 2010 (see Question 6)

1.3 Recommendations

1.3.1 Approvability

NDA 203479 is recommended for approval from the pharmacology/toxicology perspective,

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Pending satisfactory agreement with the Sponsor. Labeling changes will be summarized in separate review.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 5786-21-0

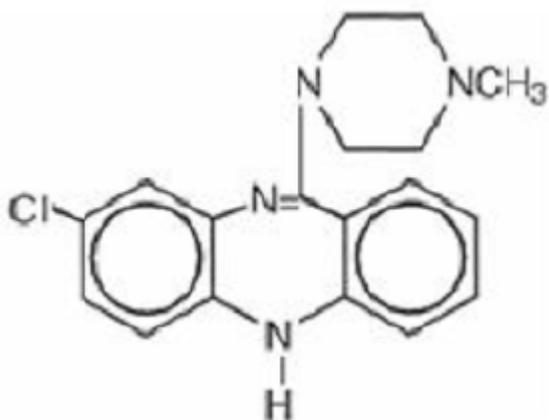
Generic Name: Clozapine

Code Name: none

Chemical Name: 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[*b,e*][1,4]diazepine

Molecular Formula/Molecular Weight: C₁₈H₁₉ClN₄/326.83

Structure:



Pharmacologic Class: atypical antipsychotic

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 108466 for clozapine oral suspension, NDA 19758 for Clozaril® (Clozapine Tablets), DMF # [REDACTED] ^{(b) (4)} for Clozapine USP drug substance

2.3 Drug Formulation

The drug product contains 50 mg/mL and is free-flowing suspension with a density of [REDACTED] ^{(b) (4)} g/mL. The quantitative composition of the suspension is provided below.

Quantitative Composition of Drug Product

Component	Grade	w/w%	Qty/Unit (mg/mL)	Commercial Batch Size (b)(4) Kg (b)(4) (kg)	Pharmaceutical Function	IID Limits ³ (oral route of administration)		
Clozapine	USP	(b)(4) %	50.00	(b)(4)	Active	N/A		
Sorbitol (b)(4)	USP	(b)(4)					(b)(4)	
Povidone (b)(4)	USP						(b)(4)	
Sodium Dihydrogen Phosphate Dihydrate	USP						(b)(4)	
Sodium Hydroxide	NF						(b)(4)	
(b)(4)	NF						(b)(4)	
Methylparaben sodium	NF						(b)(4)	
Propylparaben sodium	NF						(b)(4)	
Xanthan gum	NF						(b)(4)	
Glycerin	USP						(b)(4)	
Water	USP						(b)(4)	N/A
Total	-						(b)(4)	--

¹ May be adjusted between (b)(4)

² May be adjusted between (b)(4)

³ Information provided from FDA's Inactive Ingredient Database, last updated Oct 14, 2011.

⁴ Information provided from FDA's Inactive Ingredient Database update of Oct 22, 2010.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

The following impurities may be present in the drug substance:

Impurity	Identification
8-Chloro-5,10-dihydro-11 <i>H</i> -dibenzo[<i>b,e</i>][1,4]diazepin-11-one.	USP Monograph Impurity A
11,11'-(Piperazine-1,4-diyl)bis(8-chloro-5 <i>H</i> -dibenzo[<i>b,e</i>][1,4]diazepine).	USP Monograph Impurity B
8-Chloro-11-(piperazin-1-yl)-5 <i>H</i> -dibenzo[<i>b,e</i>][1,4]diazepine.	USP Monograph Impurity C
4-Chloro- <i>N</i> 1-(2-((4-methylpiperazin-1-yl)carbonyl)phenyl)benzene-1,2-diamine	USP Monograph Impurity D

The above specified impurities are controlled as per USP monograph specifications. All unspecified impurities are controlled at the ICH Q3A threshold of NMT 0.10%.

2.6 Proposed Clinical Population and Dosing Regimen

Management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment of schizophrenia.

2.7 Regulatory Background

On 29 June 2010, the Sponsor met with the Division. The purpose of the meeting was to ascertain the requirements for the filing and approval of a 505(b)(2) NDA for clozapine oral suspension, 50 mg/mL (see Meeting Minutes dated July 20, 2010). No additional nonclinical studies were required.

3 Studies Submitted

None

However, in support of the safety, the following information updates were submitted for the NDA 203479 for clozapine oral suspension:

Safety Update 1: Safety information summary encompassing a literature search on clozapine for the period September 1, 2009 to September 30, 2010; and AERS database search on clozapine for the period January 1, 2009 through March 31, 2010.(previously provided in IND 108466).

Safety Update 2: Safety information summary encompassing a literature search on clozapine for the period October 1, 2010 to September 30, 2011; and AERS database search on clozapine for the period April 1, 2010 through March 31, 2011*.

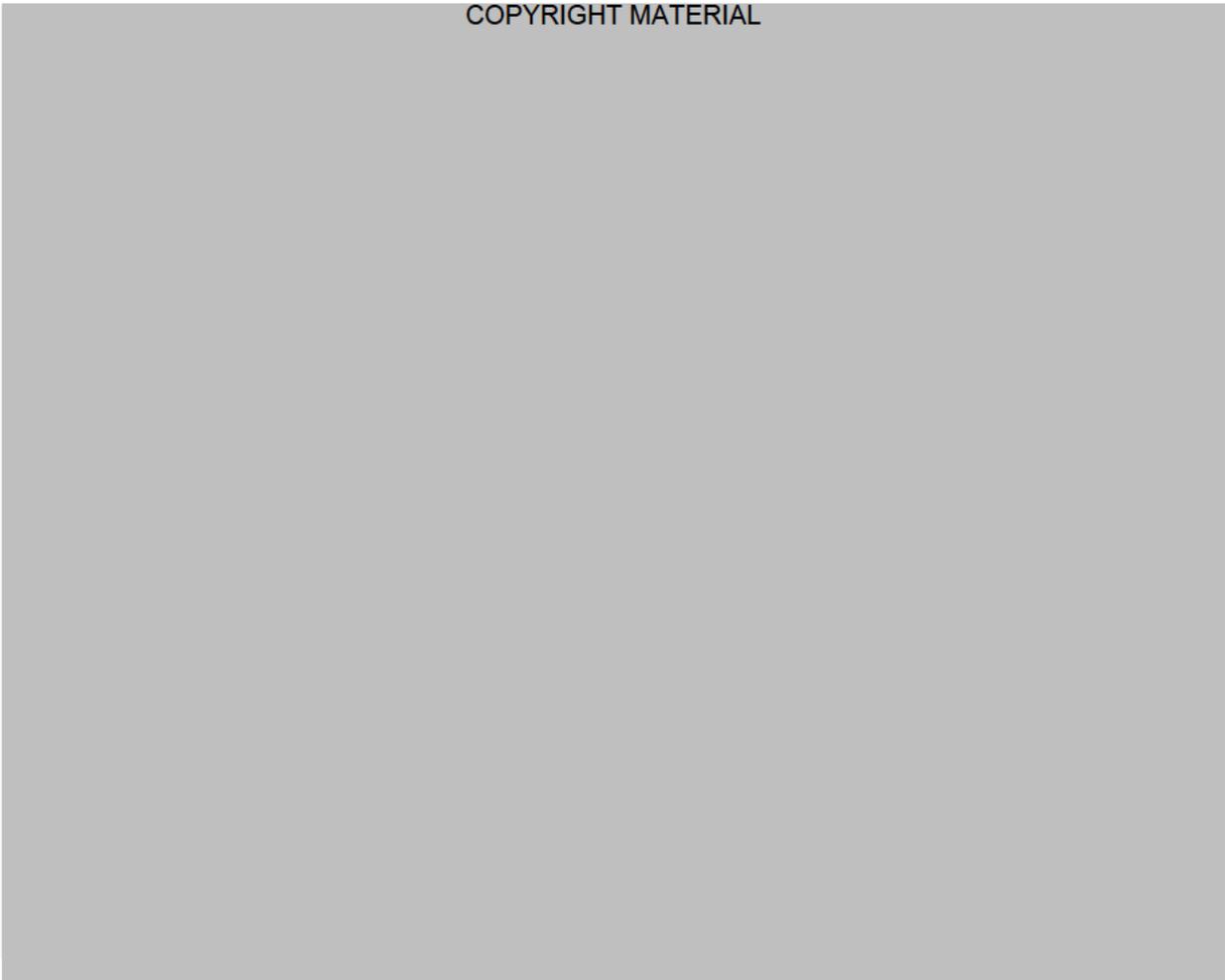
*This is the most current AERS data available from FDA at the time of submission.

There was no significant nonclinical information and no new or unexpected risks were identified in a literature and AERS database search periods listed above. Based on the proven efficacy of clozapine for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia, and its well-described safety profile, the benefit-risk for clozapine is still considered to be favorable.

Adverse reaction profiles of first (conventional) and second (atypical) generation of antipsychotic medications was provided by the Sponsor (adopted from Muench J., Hamer A.M., Adverse effects of antipsychotic medications, *Am Fam Physician*. 2010; 81(5):617-622).

Table 1: Comparison of the Adverse Reaction Profiles of First and Second Generation Antipsychotic Drugs [1]

COPYRIGHT MATERIAL



11 Integrated Summary and Safety Evaluation

The NDA 203479 provides for a change in dosage form (i.e., from an oral tablet to an oral suspension). No additional nonclinical safety data were required for this NDA as indicated in the IND 108466 Meeting Minutes dated July 20, 2010 (see Question 6).

The Sponsor has demonstrated that the proposed product is bioequivalent in rate and extent of absorption to the listed drug product Clozaril® (Clozapine Tablets), as determined by the Agency's Office of Clinical Pharmacology. In conclusion, from the pharmacology/toxicology, there is no objection to approve the NDA 203479.

Elzbieta Chalecka-Franaszek, Ph.D., Pharmacologist *{see appended electronic signature page}*

Aisar Atrakchi, Ph.D., Supervisor *{see appended electronic signature page}*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELZBIETA CHALECKA FRANASZ
10/02/2012

AISAR H ATRAKCHI
10/09/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:

NDA 203479

Applicant: Douglas

Pharmaceuticals America Ltd

Stamp Date:

December 29, 2011

Drug Name: Clozapine Oral
Suspension, 50 mg/mL

NDA/BLA Type:

505(b)(2) Application

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	N/A	N/A	This is 505(b) (2) NDA application for Clozapine Oral Suspension, 50 mg/mL, which relies on the Agency's previous finding of safety and efficacy of the listed drug Clozaril® (Clozapine Tablets), NDA 19,758. No additional nonclinical safety data were required for this NDA as indicated in the IND 108466 Meeting Minutes dated 07/20/2010 (Question 6)
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	N/A	N/A	See comment above
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	N/A	N/A	See comment above
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	N/A	N/A	
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		X	Not required
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	N/A	N/A	No additional nonclinical safety data were required for this NDA as indicated in the IND 108466 Meeting Minutes dated 07/20/2010 (Question 6)
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	N/A	N/A	See comment above
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		No issues are identified at this time. Impurity information has been submitted and is under review by the chemistry reviewer.
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	N/A	N/A	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant. **N/A**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **None**

_____ Reviewing Pharmacologist	_____ Date
Elzbieta Chalecka-Franaszek, Ph.D.	February 27, 2012
_____ Team Leader/Supervisor	_____ Date
Aisar Atrakchi, Ph.D.	February 27, 2012

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELZBIETA CHALECKA FRANASZ
02/28/2012

AISAR H ATRAKCHI
02/28/2012