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# Non-Immediate Type Hypersensitivity Reactions with First-Line Antituberculosis Drugs and Diagnostic Patch Testing

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## ABSTRACT

**Objective:** To evaluate the characteristics of non-immediate type hypersensitivity reactions with first-line antituberculosis drugs and determine the causative drugs by patch tests and drug provocation tests.

**Materials and Methods:** Baseline data including patients' demographics, disease characteristics, and drug hypersensitivity reaction characteristics were recorded. Patch testing was performed with all the drugs used during hypersensitivity reaction at 1/10 and 1/1 concentrations. Drug provocation tests were performed at 3-day intervals with drugs that had negative patch test results.

**Results:** A total of 32 patients were included in the study. The clinical phenotype was maculopapular eruption in 11(34.4%), dermatitis in 10 (31.3%), drug reaction with eosinophilia and systemic symptoms in 1 (3.1%), and Stevens-Johnson syndrome/Toxic epidermal necrolysis in 10 (31.3%) patients. Combination therapy during the index reaction consisted of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) in 28 (87.5%) patients, Patch tests were performed with 95 drugs consisting of 25 H, 25 R, 21 Z, and 24 E in 25 patients. Results were positive in 8 patients with 10 drugs: 8 (32%) H, 1 (4%) R, and 1 (4.2%) E positivity were detected. Drug provocation tests were performed with 78 drugs (18 H, 23 R, 15 Z, 22 E) in 25 patients and resulted positive with H, R, Z, and E in 16.7% (3 of 18), 21.7% (5 of 23), 46.7% (7 of 15), and 54.5% (12 of 22) of the patients respectively. Negative predictive values of patch tests with H, R, Z, and E were calculated as 87.5% (14/16), 81.8% (18/22), 50% (7/14), and 45% (9/20) respectively. According to the results of the patch tests and provocation tests, the most common culprit of hypersensitivity reactions was found to be E (n=12), followed by H (n=10). Multiple drug hypersensitivity was detected in 9 of 23 (39.1%) patients.

**Conclusion:** Patch testing is useful in the management of non-immediate type hypersensitivity with first-line antituberculosis drugs. However, further studies are needed to determine its predictive value

**Keywords:** Non-immediate, hypersensitivity, antituberculosis, patch test, drug provocation

## INTRODUCTION

Tuberculosis is a serious public health threat unless it is treated properly. A multidrug regimen including isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) is used as first-line treatment for tuberculosis. All four drugs are used in the initiation phase of treatment for 2 months and then H and R are used in the maintenance phase of treatment for 4 months (1).

All of the first-line antituberculosis drugs have the potential to cause hypersensitivity reactions ranging from mild to severe life-threatening reactions (2-4). Presentation of drug hypersensitivity reactions (DHRs) may vary.

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They can be classified based on chronology, mechanism, and clinical phenotypes. Chronologically, reactions can be classified as immediate and non-immediate/delayed reactions. Non-immediate DHRs may occur at any time from 1 h after the initial drug administration, commonly after many days or, in some cases, weeks of treatment (5,6). They are often associated with a delayed T-cell-dependent type of allergic mechanism and include clinical phenotypes such as maculopapular eruptions (MPE), dermatitis, fixed drug eruptions (FDE), symmetrical drug-related intertriginous and flexural exanthemas (SDRIFE), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and Stevens-Johnson syndrome (STS)/toxic epidermal necrolysis (TEN) (5,6).

Non-immediate type hypersensitivity reactions with antituberculosis drugs create difficulties in diagnosis and treatment. Since patients are on multiple drug regimens it is often difficult to identify the causative drug from history alone, and multiple drug hypersensitivity reactions with antituberculosis drugs are also common (7-9). Alternative therapies for tuberculosis are limited, and second-line therapy is less effective, more expensive, and has more side effects than first-line antituberculosis drugs, in addition to switching to second-line therapy prolonging the duration of treatment (4,10,11). Therefore, it is important to identify the culprit drug(s) and remove them from treatment.

Drug provocation testing is the gold standard method to confirm or rule out a DHR and identify the culprit drug. However, this approach increases the risk of inducing additional reactions and possibly a severe one. Performing epicutaneous and intracutaneous tests before drug provocation tests can sometimes give valuable information (12,13). Intradermal tests are recommended with the drugs available in sterile parenteral formulations. R is the only drug in parenteral form in our country, and this method is a limited option for our country. Patch testing can be used to identify the culprit drug causing the non-immediate type drug allergy. However, the diagnostic accuracy of patch tests with antituberculosis drugs is not exactly known.

The aim of this study was to evaluate the clinical characteristics of patients with non-immediate type hypersensitivity reactions with first-line antituberculosis drugs, and also determine the causative drugs detected by patch tests and drug provocation tests.

## MATERIALS and METHODS

### Study Population

This is a retrospective observational study of active tuberculosis patients who had non-immediate type hypersensitivity reactions with first-line antituberculosis drugs and underwent patch tests and drug provocation tests with culprit drugs from January 2012 to December 2023 at our Allergy and Clinical Immunology Clinics. The study was approved by the local ethics committee (approval number 2024-BCEK/92).

The inclusion criteria of the patients were having non-immediate type hypersensitivity reactions which were thought to be T cell-mediated with signs and symptoms such as MPE, dermatitis, FDE, SDRIFE, DRESS, AGEP, and SJS/TEN with first-line antituberculosis drugs. The exclusion criteria for the patients were insufficient medical records.

### Patients, Disease, DHR Characteristics

Baseline data including patients' demographics (age, gender, other drug allergies), disease characteristics (site of infection, diagnostic method, case definition), DHR characteristics (culprit drugs, interval between antituberculosis treatment initiation and DHR, the symptoms, any treatment interruption before DHR) were recorded.

The site of tuberculosis infection was classified as pulmonary and non-pulmonary. The diagnostic method was classified as bacteriologically confirmed if a biological specimen was positive by smear microscopy, culture, or real-time polymerase chain reaction; histologically diagnosed if the tissue biopsy sample was suggestive of caseification; and clinically diagnosed if the clinical and radiological findings were suggestive of tuberculosis infection. Case definition was classified as new cases that had never been treated for tuberculosis or had taken antituberculosis drugs for less than one month; and previously treated cases who had received one month or more of antituberculosis drugs.

### Management

In the management of the index reaction, all drugs were stopped because the offending drug could not be determined from the patient's history. Then, patients were treated with topical or systemic steroids and/or antihistamines until the lesions resolved and the laboratory pa-

rameters returned to baseline if they were deteriorated. Afterwards, patch tests were performed with all the drugs used during the hypersensitivity reaction. If continuation of treatment with first-line drugs was considered by the primary physician, drug provocation tests were performed with drugs that had negative patch test results.

**Patch Tests**

Patch tests were performed on the upper back according to previously published guidelines (13-15). Powders of commercialized drugs obtained by crushing the tablets or emptying the capsules were used to prepare patch test material. The concentrations used were 10% diluted in white petrolatum and 1/1 moistened with saline. We previously reported that these concentrations were non-irritant in 16 controls who used these drugs without any hypersensitivity reaction (16). White petrolatum was also tested as a negative control. All tests were removed after 2 days, and readings were done according to European Society of Contact Dermatitis (ESCD) criteria on the day D2 and also D3 or D4, (14,15).

The negative predictive value of patch tests was calculated by the ratio of true negative results to true negative and false negative results

**Drug Provocation Tests**

After a negative patch test, drug provocation tests were performed to confirm or exclude drug hypersensitivity. Drugs were reintroduced at therapeutic doses, one drug at a time at 3-day intervals similar to the European Academy of Allergy and Clinical Immunology/European Network for Drug Allergy (EAACI/ENDA) task force suggestions (12). On the first day, the therapeutic dose was reached with a 6- to 8-step administration protocol, and full therapeutic doses were given on the second and third days. If there was no reaction, the drug provocation test was started for the next drug. If a reaction occurred, the drug provocation test was discontinued, and the administration of the next drug was postponed until the symptoms resolved.

We previously described 6- to 8-step administration protocols applied on the first day of these schemes as a rapid desensitization protocol in immediate-type hypersensitivity reactions with first-line antituberculosis drugs (2,3).

**Culprit Drugs and Type of Drug Hypersensitivity**

Culprit drug(s) and type of hypersensitivity were defined according to the results of both patch tests and drug provocation tests. The term "multiple drug hypersensitivity" (MDH) was used when patch testing and/or drug provocation testing was done with all the drugs used in the first reaction and resulted positive for two or more drugs. The term "single drug hypersensitivity" (SDH) was used when patch testing and/or drug provocation testing was done with all the drugs used in the first reaction and resulted positive for only one drug. If the drug provocation test or patch test results were positive for one drug but provocation tests did not include all the drugs used during the first reaction, except for drugs with a positive patch test, the term "unknown" was used. MDH rate was calculated by the ratio of MDH to MDH and SDH.

**Statistical Analysis**

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows 16.0 software package (SPSS Inc., Chicago, IL, USA). We used Shapiro-Wilk's test to assess the assumption of normality for continuous variables. In the evaluation of the data, mean and standard deviation for normally distributed data, median and interquartile range for data that did not show a normal distribution, and values and percentages for the ratios were determined by the descriptive statistical method. We used the Mann-Whitney U test to compare continuous variables, and the chi-square test or the Fisher's exact test for categorical variables. A "p-value" less than 0.05 was considered statistically significant**.**

**RESULTS**

**Demographics and Disease Characteristics**

A total of 32 patients, 16 (50%) female and 16 (50%) male, with a mean age of 59.75±14.12 (range 30-81) years were included in the study. Two (6.3%) patients had other drug allergies: one had quinolone and the other had beta-lactam allergy.

The diagnosis was pulmonary tuberculosis in 18 (56.3%) and non-pulmonary tuberculosis in 14 (43.8%) patients. Tubercular lymphadenitis (n= 10, 71.4%) was the most common type of extrapulmonary tuberculosis. Other types of non-pulmonary tuberculosis according to the involved organs were the uvea, pancreas, mastoid tissue, and soft tissue tuberculosis (n=1, 7.1% each).

The diagnosis was bacteriologically confirmed in 16 (50%) patients. Fifteen (46.9%) patients were diagnosed histologically, and one patient (3.1%) was diagnosed clinically. Case definitions were new cases in 29 (90.6%) patients and previously treated cases in 3 (9.4%) patients.

**Treatment and Hypersensitivity Reaction Characteristics**

Combination therapy at the time of the index reaction consisted of HRZE in 28 (87.5%) patients, HRE in 3 (9.4%) patients, and HR in 1 (3.1%) patient. The interval between antituberculosis therapy initiation and hypersensitivity reaction was a median of 18 (range 3-100) days.

Clinical features of hypersensitivity reaction were MPE in 11 (34.4%), dermatitis in 10 (31.3%), DRESS in 1 (3.1%), and SJS/TEN in 10 (31.3%) patients. The median time for hypersensitivity reaction development was 12 (3-60) days for MPE, 14.5 (3-100) days for dermatitis, 42 days for DRESS, and 25 (7-90) days for SJS/TEN. No significant difference was observed in terms of reaction development times (p=0.243).

**Patch Tests and Drug provocation Tests**

Patch tests were performed with 95 drugs; 25 H, 25 R, 21 Z, and 24 E in 25 patients. Results were positive in 8 patients with 10 drugs; 8 (32%) H, 1 (4%) R, and 1 (4.2%) E positivity were detected. Two patients had double positivity, one with HR and one with HE. No positivity was observed with Z patch testing. Results of patch tests are shown in **Table I**. Positive results were observed with both 1/10 and 1/1 concentrations in all 5 patients for whom positive concentration data were available in their hospital files. The median interval between index reaction and patch testing was 18.5 (7-62) days.

Drug provocation tests were performed with 78 drugs (18 H, 23 R, 15 Z, 22 E) in 25 patients. Provocation tests resulted positive with H, R, Z, and E in 16.7% (3 of 18), 21.7% (5 of 23), 46.7% (7 of 15), and 54.5% (12 of 22) patients respectively. Results of drug provocation tests are shown in **Table I**.

In six patients with SJS/TEN, patch tests or drug provocation tests were not performed due to the severity of the reaction and therapy was switched to second-line antituberculosis drugs. Four patients with SJS/TEN underwent patch testing that resulted positive in one (25%) patient.

Drug provocation tests were performed in one patient with DRESS and 3 patients with SJS/TEN with 7 drugs (2 H, 3R, 2E) upon request of the primary physician. Provocation tests resulted positive with 3 drugs (1H, 2E), but no severe generalized reaction was observed in any patient.

The provocation test of the drug, which had a positive patch test, was performed in only one patient (case 1) with H and resulted in positive. Negative predictive values of patch tests with H, R, Z, and E were calculated as 87.5% (14/16), 81.8% (18/22), 50% (7/14), and 45% (9/20) respectively.

According to the results of patch tests and provocation tests, the most common culprit of hypersensitivity reactions was found to be E (n=12), followed by H (n=10), Z (n=7), and R (n=6).

MDH was detected in 9 of 23 (39.1%) patients; 5 patients had HE, two patients had HRE, and each patient had HR and HZ hypersensitivity together. H (n=9) and E (n=7) were the most common culprits of MDH reactions.

**DISCUSSION**

In this study, we evaluated the clinical characteristics of patients who had non-immediate type hypersensitivity with first-line antituberculosis drugs, and the causative drugs detected by patch tests and oral provocation tests.

There is limited data about predictive values of in vivo and in vitro diagnostic methods in non-immediate type antituberculosis drug hypersensitivity reactions. In this study, patch tests were found to be positive in 8 of 25 (32%) patients with 10 drugs; 8 H, 1 R, and 1 E. Negative predictive values of patch tests with H, R, Z, and E were calculated as 87.5%, 81.8%, 50%, and 45% respectively. These results suggest that although drug provocation tests need to be performed to determine the culprit drug, negative patch tests may be helpful to exclude H and R hypersensitivity. Provocation with a patch test positive drug was performed in only 1 patient and resulted positive with H.

There are only a few studies about non-immediate type antituberculosis drug hypersensitivity and patch test applications. Lehloenya et al. performed 204 patch tests in 60 patients with cutaneous adverse drug reactions including DRESS and SJS/TEN. They used 30% dilutions. Patch tests were positive with 17 drugs in 14 patients. Of these patients the initial reaction was DRESS in 12 and SJS/

TEN in 2 patients. Patch test positivity with H, R, Z, and E was 6,7,1, and 3 respectively. Three of the patch tests were positive for two drugs. Unfortunately, 10/11 (91%) of patients with Human immunodeficiency virus (HIV) infection developed systemic reactions to the patch tests compared with none of the HIV uninfected patients. They hypothesized that it is a manifestation of the dysfunctional drug-related immune response associated with active HIV

**Table I: Clinical phenotypes of patients and the results of patch tests and drug provocation tests.**

| Case number | Clinical phenotype | Initial therapy | Patch test results | | | | Drug provocation test results | | | | Culprit drug(s)* | Type of drug hypersensitivity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | H † | R‡ | Z§ | E‖ | H | R | Z | E | | |
| 1 | Dermatitis | HRE | + | - | NA¶ | - | + | - | NA | + | HE | Multiple |
| 2 | Dermatitis | HR | + | + | NA | NA | NA | NA | NA | + | HRE | Multiple |
| 3 | Dermatitis | HRZE | + | - | - | - | NA | + | - | + | HRE | Multiple |
| 4 | Dermatitis | HRZE | - | - | - | - | - | + | - | - | R | Single |
| 5 | Dermatitis | HRE | - | - | NA | - | - | - | NA | + | E | Single |
| 6 | Dermatitis | HRZE | - | - | - | - | - | - | NA | + | E | Unknown |
| 7 | Dermatitis | HRZE | - | - | - | - | - | - | - | + | E | Single |
| 8 | Dermatitis | HRZE | - | - | - | - | - | - | + | - | Z | Single |
| 9 | Dermatitis | HRZE | + | - | - | - | NA | + | NA | NA | HR | Multiple |
| 10 | Dermatitis | HRZE | - | - | - | - | - | + | - | - | R | Single |
| 11 | MPE ** | HRZE | + | - | - | - | NA | - | + | - | HZ | Multiple |
| 12 | MPE | HRZE | - | - | - | - | - | - | + | - | Z | Single |
| 13 | MPE | HRZE | - | - | - | - | - | - | - | + | E | Single |
| 14 | MPE | HRZE | + | - | - | - | NA | - | - | + | HE | Multiple |
| 15 | MPE | HRZE | - | - | - | - | + | - | NA | + | HE | Multiple |
| 16 | MPE | HRZE | - | - | - | - | - | - | + | - | Z | Single |
| 17 | MPE | HRZE | - | - | - | - | - | - | + | - | Z | Single |
| 18 | MPE | HRZE | - | - | - | - | - | - | + | - | Z | Single |
| 19 | MPE | HRZE | NA | NA | NA | NA | - | + | - | - | R | Single |
| 20 | MPE | HRZE | - | - | - | - | - | - | - | + | E | Single |
| 21 | MPE | HRZE | - | - | - | - | - | - | + | - | Z | Single |
| 22 | DRESS †† | HRZE | + | - | - | - | NA | - | NA | + | HE | Multiple |
| 23 | SJS/TEN ‡‡ | HRZE | - | - | - | - | NA | NA | NA | NA | | Unknown |
| 24 | SJS/TEN | HRZE | NA | NA | NA | NA | NA | NA | NA | NA | | Unknown |
| 25 | SJS/TEN | HRZE | + | - | - | + | NA | - | NA | NA | HE | Multiple |
| 26 | SJS/TEN | HRZE | NA | NA | NA | NA | NA | NA | NA | NA | | Unknown |
| 27 | SJS/TEN | HRZE | NA | NA | NA | NA | NA | NA | NA | NA | | Unknown |
| 28 | SJS/TEN | HRE | - | - | NA | - | - | - | NA | + | E | Single |
| 29 | SJS/TEN | HRZE | NA | NA | NA | NA | NA | NA | NA | NA | | Unknown |
| 30 | SJS/TEN | HRZE | - | - | - | - | + | NA | NA | NA | H | Unknown |
| 31 | SJS/TEN | HRZE | NA | NA | NA | NA | NA | NA | NA | NA | | Unknown |
| 32 | SJS/TEN | HRZE | NA | NA | NA | NA | NA | NA | NA | NA | | Unknown |

* Culprit drug(s) and multiple drug hypersensitivity are defined according to the results of patch tests and drug provocation tests, †H: isoniazid, ‡R: rifampicin, §Z: pyrazinamide, ‖E: ethambutol, ¶NA: not applicable, ** MPE: maculopapular eruption, †† DRESS: drug reaction with eosinophilia and systemic symptoms, ‡‡ SJS/TEN: Stevens-Johnson syndrome / toxic epidermal necrolysis

infection and immune dysregulation (17). In our study, none of the patients were HIV-infected or had systemic reactions to patch testing.

Allouchery et al. performed patch testing in 10 patients with DRESS secondary to antituberculosis drugs. Patch tests were found positive in 7 cases with 8 drugs. Patch test positivity with H, R, Z, and E was 5, 1, 0, and 2 respectively. Patch tests were positive in one case for both isoniazid and ethambutol. Discrepancies between epicutaneous tests and the reintroduction of the culprit drug were observed in two cases. For one case, patch tests were only positive for isoniazid; a premature reintroduction of rifampicin and pyrazinamide was complicated by a relapse of mild rash. For the other case, although all patch tests were negative, two challenge tests with ethambutol led to a cutaneous relapse with eosinophilia. None of the patch tests led to a relapse of DRESS (18).

In the study of Ban et al., patch testing with 10% dilutions were performed in 3 MPE and 5 DRESS patients due to first-line antituberculosis drugs and positive results were recorded in 1 MPE and 2 DRESS patients with 5 drugs. In the immunologic studies, a total of five (13.5%), 16 (43.2%), and 12 (32.4%) tests of 37 culprit drugs were positive in patch tests, intradermal tests, and lymphocyte transformation tests respectively. Patch test positivity with H, R, Z, and E was 1, 1, 2, and 1 respectively. Drug provocation tests with patch-positive drugs were also reported positive (19).

Oh et al. performed patch tests with 10% dilutions in 9 DRESS and 2 SJS patients. Six (66.7%) patients with DRESS and one patient with SJS had positive patch test results and all of these patients showed multiple drug hypersensitivity. Patch test positivity with H, R, Z, and E was 5, 2, 4, and 2 respectively (20).

Guidelines recommend performing drug patch tests at least 4-6 weeks after following the index reaction to avoid false negative results. However, it is not practically feasible, especially where active tuberculosis infection needs to be urgently treated. Delaying treatment of tuberculosis patients has risks of severe, disseminated disease or drug resistance (17,20-22). Unfortunately, we could not fully comply with these recommended periods in our study; the median interval between the index reaction and patch testing was 18.5 (7-62) days.

The patch test procedure with antituberculosis drugs is not standardized in current guidelines (5,12,13,23). In previous reports, different test concentrations and vehicles were used (17,19,20,24-28). Guidelines generally recommend 30% dilutions when conducting diagnostic patch testing using the drug in its commercially available formulation (13-15). In this study, we used 10% diluted in white petrolatum and undiluted, only moistened with saline concentrations of commercial drugs. We previously reported that these concentrations were non-irritant in 16 controls who were treated for tuberculosis and tolerated first-line antituberculosis drugs (16). Bakkum et al. also reported negative results in 10 healthy controls with undiluted, only moistened with water forms of commercial antituberculosis drugs (24). We observed positive results with both 1/10 and 1/1 concentrations in five patients for whom positive concentration data were available. There is a need for standardization of the procedure.

MDH is defined as DHR to at least 2 chemically and pharmacologically distinct drugs (5). MDH to first-line antituberculosis drugs is suggested to be higher when compared with other drugs. This is important because it may result in treatment failure due to a lack of using first-line treatment (8,9). In previous studies, MDH was detected at a rate of 39.3-48% in non-immediate type reactions with first-line antituberculosis drugs and the most common culprits were reported as R and E (7-9). In our study, multiple drug hypersensitivity was detected in 39.1% of patients and H and E were found to be the most common culprits.

Data on the most common culprit drug in the non-immediate type antituberculosis drug hypersensitivity differs in studies. Several studies have reported either rifampicin or pyrazinamide as the most common culprit agents for HSRs. However, these data should be interpreted cautiously owing to the relatively small size in previous reports. It is plausible that there is geographical variability about the frequency and patterns of sensitization to antituberculosis drugs and further data are needed to shed light (21).

This study has several limitations as it is a single-center and retrospective study. To prevent a longer delay in tuberculosis treatment and possible negative outcomes, patch testing was performed in shorter periods than recommended. It is not known whether this affected the performance of tests. Another limitation was drug provocation tests were not performed on patients with positive

patch testing results due to ethical considerations except for one patient, and the positive predictive value of the tests could not be clarified.

In conclusion there are various difficulties in the management of non-immediate type hypersensitivity reactions due to antituberculosis drugs. Patch testing is useful in the management but further studies are needed to determine its predictive value and to standardize its methodology.

**Conflict of Interest**

The authors have declared no conflict of interest regarding to this manuscript.

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**Authorship Contributions**

Conception and design of the study: **Gozde Koycu Buhari,** Data collection or processing: **Gozde Koycu Buhari, Sakine Nazik Bahcecioglu, Selcan Gultuna, Dilek Cuhadar Ercelebi, Senay Demir, Hatice Celik Tuglu, Onur Telli, Kurtulus Aksu,** Analysis and interpretation of the data: **Gozde Koycu Buhari, Sakine Nazik Bahcecioglu, Selcan Gultuna, Dilek Cuhadar Ercelebi, Senay Demir, Hatice Celik Tuglu, Onur Telli, Kurtulus Aksu**, Literature research: **Gozde Koycu Buhari, Sakine Nazik Bahcecioglu, Selcan Gultuna, Dilek Cuhadar Ercelebi, Senay Demir, Hatice Celik Tuglu, Onur Telli, Kurtulus Aksu**, Writing of the manuscript: **Gozde Koycu Buhari, Sakine Nazik Bahcecioglu, Selcan Gultuna, Dilek Cuhadar Ercelebi, Senay Demir, Hatice Celik Tuglu, Onur Telli, Kurtulus Aksu**, Approval: **Gozde Koycu Buhari, Sakine Nazik Bahcecioglu, Selcan Gultuna, Dilek Cuhadar Ercelebi, Senay Demir, Hatice Celik Tuglu, Onur Telli, Kurtulus Aksu**.

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