All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Maraviroc (Celsentri®▼) for treatment-experienced adults infected only with CCR5-tropic HIV-1

Pfizer Ltd

Advice No: 0709 – April 2009

Recommendation of AWMSG

Maraviroc (Celsentri®▼) is recommended as an option for use within NHS Wales for the treatment of treatment-experienced adults infected only with CCR5-tropic HIV-1, in accordance with British HIV Association (BHIVA) guidance.

AWMSG is of the opinion that maraviroc (Celsentri®▼) is not suitable for shared care within NHS Wales.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 29th April 2009

The recommendation of AWMSG is:

Maraviroc (Celsentri®▼) is recommended as an option for use within NHS Wales for the treatment of treatment-experienced adults infected only with CCR5-tropic HIV-1, in accordance with British HIV Association (BHIVA) guidance.

AWMSG is of the opinion that maraviroc (Celsentri®▼) is not suitable for shared care within NHS Wales.

ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
ARV	Antiretroviral
AWMSG	All Wales Medicines Strategy Group
BD	Twice daily
BHIVA	British HIV Association
CCR	Chemokine receptor
CI	Confidence interval
CLcr	Creatinine clearance
CYP3A4	Cytochrome P450 3A4
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
FAS	Full Analysis Set
GSS	Genotypic susceptibility score
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
MACS	Multi-centre AIDS Cohort Study
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitors
OBT	Optimised background therapy
OD	Once daily
OR	Odds ratio
OSS	Overall sensitivity score
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RNA	Ribonucleic acid
SPC	Summary of Product Characteristics

2.0 PRODUCT DETAILS

2.1 Licensed indication

Maraviroc (Celsentri®▼), in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable.

This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials in treatment-experienced patients[1].

2.2 Dosing

Before taking maraviroc it has to be confirmed that only CCR5-tropic human immunodeficiency virus (HIV)-1 is detectable (i.e. CXCR4 or dual/mixed tropic virus is not detected) using an adequately validated and sensitive detection method on a newly drawn blood sample. The viral tropism cannot be safely predicted by treatment history and assessment of stored samples[1]. Changes in viral tropism occur over time in HIV-1 infected patients. Therefore, there is a need to start therapy shortly after a tropism test[1].

Maraviroc is taken orally. The recommended dose is 150mg, 300mg or 600mg twice daily, depending on interactions with co-administered antiretroviral therapy and other medicinal products. It should be taken as part of an antiretroviral combination regimen and should optimally be combined with other antiretrovirals to which the patient's virus is sensitive. Physicians should ensure that appropriate dose adjustment of maraviroc is made when co-administered with cytochrome P450 3A4 (CYP3A4) inhibitors and/or inducers, since maraviroc concentrations and its therapeutic effects may be affected. Maraviroc should be used with caution in patients with renal impairment (creatinine clearance [CLcr] < 80mL/min) who are taking potent CYP3A4 inhibitors. Full details are provided in the Summary of Product Characteristics (SPC)[1].

2.3 Market authorisation date

The European Medicines Agency (EMEA) granted marketing authorisation 18th September 2007[2].

2.4 UK Launch date

Maraviroc was launched in the UK 19th November 2007[3].

3.0 DECISION CONTEXT

Most people infected with HIV-1 who start highly active antiretroviral therapy (HAART) will experience good virological responses to treatment. However, due to a range of factors, including pre-existing or newly developed antiretroviral resistance, responses may fail over time and subsequent regimens may be progressively less likely to produce a durable virological response. Highly pre-treated patients may not achieve the goals of undetectable and durable HIV plasma viral load suppression and immunological improvement[4].

The British HIV Association (BHIVA) guidelines state that in treatment-experienced patients with therapy options, the physician should construct a new HIV treatment that includes at least two (preferably three) active agents guided by HIV resistance testing and by the patient's previous antiretroviral drug history. The use of an agent from a new class is likely to be more effective[4]. In treatment-experienced patients with few or no therapy options, especially if the CD4 cell count is well maintained, it may be better to wait to change treatment until investigational agents are available that can be put

together with drugs, which may have only partial activity at best, to increase the likelihood of constructing a virologically suppressive and durable regimen[4].

For HIV to enter a cell it needs to bind to both the CD4 receptor and a co-receptor. The chemokine receptors (CCRs), CCR5 and CXCR4, are co-receptors and different HIV forms may interact specifically with just one or with both of these[2]. Maraviroc is the first of a new class of agent that selectively binds to the CCR5 co-receptor, preventing CCR5-tropic HIV-1 from entering cells. Without cell entry, the virus cannot reproduce and the number of CD4 cells increases, improving immune function[5]. Maraviroc has no antiviral activity in vitro against viruses that can use CXCR4 as their entry co-receptor (either CXCR4-tropic or dual-tropic viruses)[1]. Therefore, prior to the initiation of maraviroc therapy, it must be established that the patient has only CCR5-tropic HIV-1 detectable (i.e. CXCR4 or dual/mixed tropic virus not detected)[1]. There is currently only one validated assay to determine HIV-1 tropism, the Trofile™ assay[6], although other assays are in development[1]. To produce clinically reliable results, the assay requires the patient's viral load to be ≥1,000 copies/mL. Samples have to be shipped frozen to a laboratory in the USA and it can take up to four weeks to obtain results[6].

Acute HIV-1 infection is almost exclusively associated with CCR5 strains. CCR5 viruses also predominate during most of the chronic stage of the disease, although CXCR4 variants eventually emerge in 40 to 60% of HIV-1-positive individuals[7]. CXCR4 has been associated with immunological deterioration in the natural course of HIV infection, although a causal relationship has not been established[2].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

MOTIVATE 1 and 2 were 48 week, randomised, double-blind, placebo-controlled phase IIb/III trials conducted in heavily pre-treated adults with CCR5-tropic virus only, who had a viral load (plasma HIV-1 ribonucleic acid [RNA]) ≥5,000 copies/mL. Patients received maraviroc 300mg once or twice daily dose equivalent, or placebo, in addition to open-label optimised background therapy (OBT). A once daily dose of maraviroc is not licensed and therefore this group is not further discussed here. Individual and pooled results indicate that maraviroc produced statistically and clinically significant reductions in HIV-1 RNA viral load at 24 weeks, which were maintained at 48 weeks. The proportion of patients achieving a viral load <50 copies/mL (undetectable HIV-1 virus) was also significantly greater with maraviroc treatment than with placebo (45.5% versus 16.7% at 48 weeks, p<0.0001; 40% versus 7% at 96 weeks, p value not provided). Maraviroc treatment led to significantly greater increases in CD4 cell counts at both 24 and 48 weeks, although the increase was not significant at 96 weeks. There were no significant safety concerns noted in the trials but only limited data currently exist in relation to the potential for immune dysfunction, such as development of malignancies. Maraviroc is a substrate of the CYP 450 enzyme system and P-glycoprotein. It has a high potential for clinically significant interactions and dose adjustments may be required.

4.2 Review of the evidence on cost-effectiveness

A Markov model-based cost utility analysis of maraviroc 300mg twice daily plus OBT versus OBT alone, in the MOTIVATE studies patient population, is presented. This combines virological response data from these studies with data from a range of other sources to determine patients' transitions through CD4 cell count-defined health states.

In the base case analysis, the model estimates the incremental cost per quality-adjusted life year (QALY) gained with the addition of mariviroc to OBT to be £22,045. This is based on a gain of 1.92 QALYs and incremental costs of £42,326. However, there are a range of assumptions used in the base case model, which collectively would seem to introduce some uncertainty in to the estimate. The model is sensitive to assumptions around utility weights and the costs of OBT. Probabilistic sensitivity analysis (PSA) suggests that the probability of maraviroc being cost effective at a willingness to pay threshold of £30,000 per QALY is 99%. At a threshold of £20,000 per QALY, the probability is estimated to be 3%.

5.0 LIMITATIONS OF DECISION CONTEXT

- Patients in the MOTIVATE studies were heavily pre-treated; over 50% had ≤1 active drug in their OBT[2]. The impact of treatment with maraviroc in patients who are less treatment-experienced is unclear.
- The patient population studied in the pivotal trials was quite homogenous; the vast majority of patients were middle-aged white men, with HIV subtype B, and there were few patients with hepatitis B or C co-infection, or cardiovascular disease. Further data is warranted in subpopulations and wider patient groups[2].
- Few patients had tipranavir or darunavir included in their OBT. The OBTs in the MOTIVATE studies may therefore not fully reflect the current treatment regimens used for highly pre-treated patients in practice today.
- CCR5 blockade carries a potential risk for immune dysfunction (infections, auto-immune disorders, malignancies) and the available safety data is too limited to determine the long term risks.

6.0 CLINICAL EVIDENCE

The company submission provides details of two identical phase IIb/III trials conducted in treatment-experienced patients with CCR5-tropic virus (MOTIVATE 1 and 2) and one supportive study conducted in patients with CXCR4-tropic virus (study A4001029). This last study does not meet the licensed indications for maraviroc, so is not discussed under the efficacy section.

6.1 Clinical efficacy

MOTIVATE 1 (conducted in USA, Canada and Puerto Rico) and MOTIVATE 2 (conducted in Australia, USA and Europe, including 11 sites in the UK[3]) were 48 week, randomised, double-blind, placebo-controlled trials[2,8], with an open-label follow up at 96 weeks (available as abstract)[3,9,10]. For inclusion, treatment-experienced adults with CCR5-tropic virus only were required either to have been treated for at least six months with at least one drug from three of the four antiretroviral drug classes (nucleoside or nucleotide reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs] or entry inhibitors) (two drugs in the case of PIs) or to have documented resistance to three of the four classes. They were also required to have a viral load (plasma HIV-1 RNA) $\geq$5,000 copies/mL and to have a stable pre-study antiretroviral regimen or no antiretroviral agents for 4 weeks.

Patients were randomised to maraviroc 300mg twice daily dose equivalent or placebo, in addition to open-label OBT with three to six antiretroviral drugs that was determined by a clinical investigator based on the results of resistance testing, treatment history and safety/tolerability considerations. A third group received maraviroc 300mg once daily dose equivalent but, as this dose is not licensed, this group is not further

discussed here. After two weeks of treatment the OBT could only be changed for reasons of toxicity. Patients whose OBT included PIs (around 80%[3]) received an adjusted maraviroc dose (150mg twice daily), due to the increased exposure of maraviroc observed in the presence of these agents[2,8].

The primary endpoint of the trials was mean change in viral load (log_{10} HIV-1 RNA) from baseline to week 48, with a pre-specified interim analysis at 24 weeks[3]. Secondary endpoints included the percentage of subjects with viral load <400 copies/mL and <50 copies/mL, and differences in the magnitude of changes in CD4 cell counts from baseline to weeks 24 and 48. Patients were stratified at randomisation by baseline viral load (<100,000 or ≥100,000 HIV-1 RNA copies /mL)[2] and the use of enfuvirtide[6]. All analyses presented were conducted on the Full Analysis Set (FAS) population, which included all randomised patients who received at least one study drug dose.

There were no relevant differences in baseline characteristics, proportion of dropouts and outcomes between MOTIVATE 1 and 2[2,8]. Therefore, results of the pooled analyses (FAS – As treated) are provided in Table 1A, Appendix 1. These indicate that maraviroc produced statistically and clinically significant reductions in HIV-1 RNA viral load at 24 weeks, which were maintained at 48 weeks, when added to OBT. The proportion of patients achieving a viral load <50 copies/mL (undetectable HIV-1 virus) was also significantly greater with maraviroc treatment than with placebo (45.5% versus 16.7% at 48 weeks, p<0.0001; 40% versus 7% at 96 weeks, p value not provided). Maraviroc treatment led to significantly greater increases in CD4 cell counts at both 24 and 48 weeks although the increase was not significant at 96 weeks[3,9,10].

A *post hoc* subgroup analyses was undertaken in the population with an overall sensitivity score (OSS) of two (see glossary). HIV-1 RNA viral load and change in CD4 cell count from baseline favoured subjects randomised to the maraviroc arm at both 24 and 48 weeks[3]. The trial does not, however, appear to have been statistically powered to make these comparisons.

Pre-specified and *post hoc* subgroup analyses explored the influence of baseline viral load, baseline CD4 cell count and the number of active drugs in the patients' OBTs based on genotypic susceptibility scores (GSS [see Table 2A, Appendix 1]). These indicate that, in both the maraviroc and the placebo group, there was a greater proportion of responders in those with lower baseline HIV-1 RNA levels (<100,000 copies/mL), those with higher baseline CD4 counts and those with more active drugs in the OBT. Maraviroc was consistently more effective at reducing viral load to undetectable levels (<50 copies/mL) than placebo.

At 24 weeks, 63.6% of the placebo group had discontinued treatment, compared with 32.4% of the maraviroc group. The main reason for discontinuation was lack of efficacy in both groups (50.7% of the placebo group, 21.4% of the maraviroc group)[2]. This was reflected from baseline to week 48 (54% versus 23%) and from week 48 to week 96 (22% versus 2%)[3]. The majority of patients failing with maraviroc showed CXCR4 virus at rebound (56%, with a further 14% not typeable) while the vast majority failing with placebo still had CCR5 virus (90%). When stopping maraviroc treatment, 30/44 reverted back to CCR5 virus[2].

Points to note:

- Of patients eligible for screening for the MOTIVATE studies, around 45% were excluded due to the presence of CXCR4 virus. This underlines the central role of a valid and sufficiently sensitive assay[2].
- The patient population studied was quite homogenous; the vast majority of patients were middle-aged white men, with HIV subtype B. There were few patients with hepatitis B or C co-infection (approximately 5%), or cardiovascular disease.
- Patients had received a first diagnosis of HIV approximately (mean) 14 years before study entry and were heavily pre-treated. Over 50% of patients had ≤1 drug in their OBT considered to be active as measured by GSS[2].
- Around 80% of patients received maraviroc at a dose of 150mg twice daily, due to the inclusion of PIs in their OBT.
- The use of darunavir (Prezista®) and tipranavir (Aptivus®) in the OBT was very low (only around 14% were using tipranavir and one patient in the placebo group used darunavir)[3]. These PIs were recently licensed on the basis of their efficacy in heavily pre-treated patients with demonstrated resistance to several other PIs[11,12].

6.2 Safety

In the MOTIVATE studies, median exposure to maraviroc twice daily was 239 days, compared with 145 days for placebo. This increased to 913 and 255 respectively for the 96 week follow up[10]. The available data indicate that adverse events were generally similar in frequency in patients receiving maraviroc or placebo, and were considered to be as expected in this treatment population[2]. The frequency of treatment-related adverse events was similar between treatment arms at week 48, the most common across all maraviroc recipients (those receiving once daily and twice daily maraviroc) and placebo recipients being diarrhoea (10.8% versus 12.0%, respectively), nausea (10.7% versus 11.5%), fatigue (6.5% versus 7.7%) and headache (8.5%, versus 10.0%)[2]. The corresponding data at 96 weeks was not presented.

As CCR5-mediated signalling is involved in inflammatory responses at several levels, its inhibition by maraviroc carries a potential risk for immune dysfunction (infections, auto-immune disorders, malignancies). Upper respiratory infections and mucocutaneous herpes simplex were reported to be more common with maraviroc compared to placebo based on exposure adjusted data that is not presented[2]. At weeks 24, 48 and 96, the frequencies of acquired immune deficiency syndrome (AIDS)-defining events and malignancies were similar between groups, and auto-immune disorders were not reported[2,3,9,10]. Exposure, however, is still short in relation to the development of malignancies, and a safety registry is proposed as part of the risk management plan[2].

There were no significant differences in grade 3 or 4 hepatic adverse events between maraviroc and placebo at week 24 and 48. Six patients receiving maraviroc and none receiving placebo experienced serious cardiac adverse events. These patients had significant risk factors for cardiovascular disease. As patients with serious hepatic or cardiac disease were excluded from the trials in the most part, further data are required[2]. There were 30 deaths reported up until data cut off, of which one was considered related to treatment. After adjustment for exposure time, there was no significant difference in the frequency of deaths between treatment groups[2].

Maraviroc was well tolerated, with a similar low number of patients discontinuing the main studies due to adverse events as in the placebo arms at 24 and 48 weeks.

Indeed, the cumulative percentage was slightly lower for the maraviroc arm at 96 weeks as compared to placebo (5% versus 10% respectively)[3,10].

Maraviroc should be used with caution in patients with renal impairment (CLcr <80mL/min) who are taking potent CYP3A4 inhibitors[1]. Please refer to the SPC for further information on dose adjustments and monitoring.

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Maraviroc is the first CCR5 antagonist to reach the market. It should be taken as part of an antiretroviral combination regimen and should optimally be combined with other antiretrovirals to which the patient's virus is sensitive[1]. Currently, there are no appropriate comparator medications when used for its licensed indications.

7.2 Clinical effectiveness issues

Before initiating maraviroc, it must be established that patients are infected with the CCR5-tropic virus only. The assay currently available (Trofile™) requires samples to be shipped to the USA and there is a wait of around four weeks for results to be obtained[6]. HIV-tropism can change over time, as demonstrated by the eight percent of patients who were negative for CXCR4-virus at screening for the MOTIVATE studies but were found to be CXCR4- positive at baseline around six weeks later (in the absence of selection pressure from maraviroc)[2].

The Trofile™ assay requires plasma samples from patients with viral loads ≥1,000 copies/mL[6]. Therefore, there are no data regarding the switch from a drug of a different antiretroviral class to maraviroc in virologically suppressed patients[1].

Patients in the MOTIVATE studies were heavily pre-treated. Over 50% had ≤1 drug in their OBT considered to be active as measured by GSS[2]. The MOTIVATE studies do not provide data on the use of maraviroc in less treatment-experienced patients. A large phase III study (MERIT) has compared maraviroc against efavirenz, both in combination with zidovudine/lamivudine, in antiretroviral-naive patients with CCR5-tropic HIV-1 (i.e. outside the current licensed indication). This study found maraviroc to be non-inferior in achieving viral loads <400 copies/mL; however, it failed to meet the endpoint for <50 copies/mL. Patients in the Southern Hemisphere (Argentina, South Africa, Australia) had a lower response rate to maraviroc than those in the Northern Hemisphere (North America, Europe), which the investigators speculated could be due to differences in viral types and inadvertent enrolment of non-CCR5-tropic patients[6,15]. Although HIV RNA reduction did not meet both non-inferiority margins, CD4 count increase was significantly greater in the maraviroc arm. The impact of treatment with maraviroc in patients who are less treatment experienced remains unclear.

Only low numbers of patients used darunavir or tipranavir in their OBTs in the MOTIVATE studies. These agents were recently licensed, and were recommended for use in NHS Wales by the All Wales Medicines Strategy Group (AWMSG), for use in heavily pre-treated patients, many of who will have had demonstrated resistance to several PIs[11,12,16,17]. With this in mind, the extent to which the OBTs used in the patient populations of the MOTIVATE studies will reflect those used in similar patients in Wales is unclear.

In patients who failed on maraviroc treatment, the majority showed CXCR4 virus at rebound (56%, with a further 14% not typeable), while the vast majority failing with placebo still had CCR5 virus (90%). When stopping maraviroc treatment, 30/44

reverted back to CCR5 virus[2]. Data were presented to the Scientific Advisory Group (SAG) HIV/Viral Diseases on request of the Committee of Medicinal Products for Human Use (CHMP). Due to the lack of availability of sufficient information, the experts would not recommend the re-use of CCR5-antagonists, including maraviroc, in patients who fail with CXCR4 virus and revert back to CCR5. The experts recommended that the SPC contain information about the fact that maraviroc and other CCR5-antagonists should not be used in such patients.

There is potential for many drug interactions when maraviroc is combined with other antiretroviral agents and other agents that are commonly used in the management of HIV-1 patients. Dose adjustment may be required (as in 80% of patients in the MOTIVATE studies who had PIs included in their OBT). The SPC details many of these interactions and the required dose adjustments[1].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether any additional benefits offered by the use of maraviroc in combination with OBT justify any associated increase in costs over the relevant comparator of OBT alone and, if so, whether the total budgetary impact of supporting the use of maraviroc is acceptable.

8.2 Description and critique of the company's submission

The company submission[3] describes a cost utility analysis based on a Markov cohort model. Six health states based on CD4 cell count (CD4I to CD4VI, i.e. best to worst health respectively) are described, along with the state of death. Patients may transit between the health states based on their CD4 count, which is linked to their HIV RNA level that determines treatment success or failure. When patients experience treatment success they may move to a better health state or stay in their current health state (depending on whether they exceed the threshold cell count for the next health state or not). When patients experience treatment failure, the CD4 count declines and patients may remain in their current health state or move to a worse health state. It is assumed that patients who experience failure remain on their OBT but discontinue maraviroc. For any given CD4 cell count, patients have a monthly risk of developing an opportunistic infection or AIDS-defining event. Patients also have risk of drug-related toxicity or death (either AIDS or non-AIDS related).

Data from the MOTIVATE studies has been used to categorise patients as treatment successes or failures, based on HIV RNA levels achieved with maraviroc or placebo, which determines how patients transit between the CD4-defined health states[3]. All other transition probabilities based on CD4 state are estimated and assumed from other published data. A number of uncertainties exist in the assumptions used in the base case analysis. The probability of experiencing treatment success (defined by virological response) is assumed to be the same in each of the first six months, and then in each of the next six months. The rate of increase in CD4 cells estimated between week 8 and week 48 in the MOTIVATE studies was assumed to remain constant beyond 48 weeks in those deemed to have been treated successfully[3], which is not supported by data but has been tested in supplementary sensitivity analyses. There are also some potential issues with the costs of HIV-related care that have been assumed in the base case analysis. The collective impact of these assumptions is unclear. The model has been provided by the company.

8.3 Population

The modelled population is the same as that of the combined MOTIVATE studies (receiving maraviroc twice daily or placebo)[3]. Maraviroc recipients were heavily pre-treated and had assay confirmed CCR5-tropic HIV-1. The vast majority of patients were middle-aged white men, with HIV subtype B, and there were few patients with hepatitis B or C co-infection, or cardiovascular disease. The extent to which these patients match the HIV population in Wales is a source of uncertainty.

8.4 Perspective and time horizon

The model considers the cost effectiveness of maraviroc from the perspective of NHS Wales. A 26 year (312 months) time horizon has been specified for the analysis, which given that the mean age of patients in the MOTIVATE 1 and 2 studies was around 46 years (range 21-73 years)[13,14] is likely to capture the majority of the relevant lifetime costs and outcomes of patients. However, a lifetime horizon would be appropriate. Each Markov cycle is one month, with events assumed to occur at the midpoint of each cycle. Half cycle correction has been used[3].

8.5 Comparator

Maraviroc plus OBT is compared with OBT alone. As maraviroc is currently the only licensed CCR5 antagonist, this would seem appropriate[3]. The efficacy of the OBTs assumed in the model is based on those of the MOTIVATE studies. Only low numbers of patients used darunavir or tipranavir in their OBTs in the MOTIVATE studies. These agents were recommended for use in NHS Wales by AWMSG, for use in heavily pre-treated patients, many of who will have had demonstrated resistance to several PIs[11,12,16,17]. Therefore, the efficacy of the OBTs assumed in the model may not fully reflect that of the possible OBTs that would be used in this heavily pre-treated patient population in Wales (although this would be the case across both arms that are modelled). The assumed costs of the OBTs in the model is reportedly not based on those of the agents in the OBTs of the MOTIVATE studies (see section 8.7.1).

8.6 Clinical inputs

8.6.1 Efficacy data

8.6.1.1 Probability of treatment success

The probabilities of treatment success for the maraviroc arm at six months and 12 months are based on the HIV RNA response rate (proportion of patients achieving a viral load <400 copies/mL) in the combined MOTIVATE studies at 24 weeks and 48 weeks, respectively. As there was a decline in the proportion of patients achieving virological suppression between weeks 24 and 48 in both arms of the trials, it is assumed that the probability of experiencing treatment success is the same each month during the first six months based on the 24 week data, and is the same each month in the second six months based on the 48 week data. The MOTIVATE data do not provide any rates of treatment failure beyond the first year. It is therefore assumed that the rate of failure (or probability of continued treatment success) between 24 and 48 weeks persists after the first year[3], which may be a source of bias in the model.

Lifelong treatment with maraviroc is possible in those who do not experience treatment failure in the model. Maraviroc treatment is discontinued in those who experience treatment failure (HIV RNA levels >400copies/mL) and treatment is assumed to continue with only OBT[3].

8.6.1.2 CD4 cell counts

Increases in CD4 cell counts are based on the mean increase observed in the MOTIVATE studies, rather than each of the six individual CD4 cell count categories, due to the low number of patients in each category. The CD4 cell counts are reported to have increased rapidly in the first eight weeks, and then slowed from week eight to

48, with the latter rates determined by regression analysis using the month of each CD4 cell change observation as covariate. The increase in CD4 rate is assumed to continue at the same rate after 48 weeks of treatment[3], which would seem to be a potential source for bias in the model. This assumptions has been tested in supplementary sensitivity analyses provided by the company.

Decreases in CD4 cell count define disease progression as it determines the risk of AIDS defining events and opportunistic infections. It is assumed that after a patient fails treatment the CD4 count starts to decline at a rate that is independent of the type of treatment received before failure. The rate of decline is assumed to be dependent on the mean pre-treatment viral load at baseline prior to treatment initiation (called the viral load set point). In the MOTIVATE studies, this was around 4.85 $\log_{10}$ copies/mL[3], which is around 71,000 copies/mL. Based on previous antiretroviral treatment studies, the monthly rate of CD4 cell decline has been reported as 6.375 cell/mm^3 for viral load set points between 30,000 and 100,000 copies/mL, ranging down to 3.025 cells/mm^3 for <500 copies/mL[18]. A time lag of 12 months has been incorporated between the time of virological failure and the onset of the CD4 cell decline[3].

The monthly rates of CD4 increase and decrease were used to derive transition probabilities of moving to higher or lower adjacent CD4-defined health states[3].

8.6.1.3 Mortality

In the model, monthly probabilities of dying have been calculated for death due to chronic HIV, an AIDS defining event, or other causes. All cause mortality is taken from Welsh life tables. As mortality in the MOTIVATE studies was low, HIV mortality rates based on CD4 strata have been obtained from published data from the EuroSIDA study, which is a multinational, prospective, observational cohort study to examine the impact of antiretroviral treatment on HIV-related morbidity and mortality[19]. Mortality associated with AIDS defining events is reportedly taken from another published cohort study (Multi-centre AIDS Cohort Study, MACS), which relates to the time period prior to the use of HAART. Mortality due to AIDS defining events may be overestimated from this study, and it is not clear how the data have been derived from the references provided. Sensitivity analysis has been conducted on the mortality rates associated with AIDS defining events[3].

8.6.1.4 Probability of AIDS defining events

EuroSIDA data has been used to derive the monthly probability of AIDS defining events by CD4 cell count[19], as there were too few events observed over the limited follow-up of the MOTIVATE studies to stratify by CD4 cell count[3]. Comparison of the one year risk of AIDS defining events predicted by the EuroSIDA data and observed 48 week risk in the MOTIVATE studies indicates that the EuroSIDA data underestimate the risk, especially in the placebo group. Therefore, this would seem to be a source of uncertainty or potential bias in the model. This parameter was explored by sensitivity analysis[3].

8.6.2 Adverse events

The combined MOTIVATE data have been used to provide the rates of treatment-related grade 3 or 4 serious adverse events. The data indicate that most serious adverse events occur in the first 24 weeks; therefore, it is assumed in the model that serious adverse events only occur during the first year. Furthermore, it is assumed that experiencing a serious adverse event did not have any impact on discontinuations[3].

It should be noted that the MOTIVATE studies involved few patients with liver disorders or cardiovascular disorders. The European Public Assessment Report (EPAR) notes that the 48 week follow up was insufficient to determine the influence of CCR5

blockade on immune function and the potential for development of malignancies or AIDS defining events, etc.[2] (see section 6.2).

8.6.3 Utility weights

Utility weights associated with each CD4-defined health state are derived from those assumed in a cost effectiveness analysis of two HAART regimens[20]. Utility weight associated with an AIDS defining event is taken as the mean of those reported in a cost effectiveness analysis of prevention of AIDS-related opportunistic infections[21]. This value is less than the utility values associated with any of the CD4-defined health states; therefore, all patients experiencing an AIDS defining event are assigned the lower utility weight for the duration of the cycle of the event and then in subsequent cycles are assigned the CD4-defined health state utility weight. A utility decrement of 0.14 is applied to all utilities of a cycle in which a serious adverse event occurs, based on expert opinion[3]. The impact of utility values is explored in sensitivity analyses.

8.7 Healthcare resource utilisation and cost

8.7.1 Drug and assay costs

The OBT costs used in the model are assumed to be the same in each arm and are reportedly based on the annual cost of two active agents as observed in the London area, plus the costs of etravirine use in 43% of patients (as was observed in the combined MOTIVATE trial patient populations). Sensitivity analysis has been conducted on the costs of OBT.

For the maraviroc arm, the costs are composed of the OBT cost plus the cost of maraviroc 300mg twice daily (£18.37 per day[22]) plus the cost of the Trofile™ assay. The assay costs are adjusted to account for those patients who undergo testing but do not have CCR5-tropic HIV-1 only. This is done by assuming the proportion of patients who had CCR5-tropic virus only among those who were screened for the MOTIVATE studies (56%) is the same in the modelled population. The cost per positive test is therefore the cost of the test (reported as £150) /0.56 = £268. The proportion of patients with only CCR5-tropic HIV-1 detectable is explored in sensitivity analysis[3].

8.7.2 Adverse event costs

Serious adverse events are simply assumed to require one overnight hospital stay, at a cost of £440. This is due to the fact that a wide range of adverse events were reported and it is not possible to accurately cost these[3]; however, this may be a source of uncertainty in the model. Sensitivity analysis has been performed by exploring the impact of a significant increase in the cost of adverse events (to £5,000) in the model.

8.7.3 Other resource use and costs

Routine HIV care is assumed to include the costs of managing AIDS defining events and HIV-related care.

The costs of an AIDS defining event is based on the mean of those considered in a cost effectiveness analysis of genotypic resistance testing in patients with extensive prior antiretroviral treatment[23], which is converted to £Sterling and inflated to 2007 values[3].

HIV-related care costs are based on those reported for a sample of 235 individuals between 1992 and 1993[24]. The costs of patients with asymptomatic HIV, symptomatic HIV and AIDS from this sample of individuals have been inflated to 2007 values and have been reduced by 50% before being applied to the CD4-defined health states[3]. It appears that CD4 states I to III (CD4 cell counts >200) are assumed to be asymptomatic HIV, those in states IV and V are symptomatic HIV, and those in state VI are symptomatic AIDS patients. The reason for assuming only 50% of these costs is

that company considers that there may be an element of double-counting in relation to the costs of antiretrovirals and the management of AIDS-defining events[3]. This has been explored in sensitivity analysis, but there are some uncertainties with the use of the costs of resource use in 1992 to 1993, which was pre-HAART and may not be representative of resource use today.

The costs of AIDS defining events and the costs of HIV-related care have been explored in sensitivity analyses..

8.8 Discounting

Costs and outcomes are discounted at 3.5%[3], which is the preferred discount rate.

8.9 Results

8.9.1 Base case analysis

In the base case analysis, the model estimates the incremental cost per QALY gained from adding maraviroc to OBT compared with OBT alone to be £22,045. This is based on a gain of 1.92 QALYs and incremental costs of £42,326[3].

8.10 Sensitivity analysis

8.10.1 One way sensitivity analyses

A range of one way sensitivity analyses were conducted, which indicate that the model is relatively insensitive to the assumptions around the proportion of patients who test positive for CCR5-tropic virus only (i.e. the Trofile™ assay cost per positive patient), the cost of adverse events, the monthly costs associated with each CD4-defined health state, the 24 week maraviroc treatment success rates, the costs of HIV-related care and AIDS-defining events, and the risk of AIDS defining events and deaths. Supplementary analyses provided by the company indicate that if the CD4 cell count increase is assumed to be 0% after 48 weeks of treatment, rather than being assumed to be the same as between weeks 8 and 48 weeks of treatment, the incremental cost effectiveness ratio (ICER) increases marginally to £25,600/QALY. The model was relatively sensitive to the cost of OBT, which when increased to 1.5 times that assumed in the base case analysis resulted in an ICER of £27,759[3].

The model is sensitive to the utility weights that are assumed. When the utility values are reduced by 30% and 50%, the estimated incremental cost per QALY gained increases to £31,774 and £45,020, respectively[3]. There are no analyses which consider maraviroc at a dose of 600mg twice daily, such as may be required in patients taking efavirenz in the absence of a PI[1].

8.10.2 Probabilistic sensitivity analysis (PSA)

Appropriate distributions were fitted to the model parameters to allow sampling for a probabilistic sensitivity analysis. Based on 1,000 simulations, the company submission reports that the probability of the cost per QALY falling below £30,000 is 99%, and below £25,000 is 89%[3]. The model provided by the company indicates that, at a willingness to pay threshold of £20,000/QALY, the probability of maraviroc being cost effective is 3%.

8.10.3 Scenario analysis

A scenario analysis has been reported, in which only patients with an overall sensitivity score of 2 (i.e. the total number of drugs in the OBT considered to be active by resistance testing = 2) are considered. In these patients, the incremental cost per QALY gained for maraviroc plus OBT compared with OBT alone is estimated as £20,954, based on incremental costs of £83,242 and a gain of 4.00 QALYs[3].

8.11 Review of published evidence on cost-effectiveness

A US-based cost effectiveness analysis of maraviroc plus OBT versus OBT alone has been conducted using 24 week data from the MOTIVATE studies[25]. This used a Markov microsimulation model of HIV/AIDS progression. The US maraviroc cost of $29 per day and tropism test cost of $1,960 were used, with HIV care costs taken from published HIV Research Network data and utility weights based on two published US surveys. This model estimated the incremental cost per QALY to be $66,351 based on incremental costs of $23,545 and a gain of 0.355 QALYs. These health care and tropism assay costs are somewhat different, and the estimated QALY gains are significantly lower, than those in the current model. The collective differences between the US-based model and the Welsh model precludes direct comparisons.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

The budget impact analysis uses Welsh prevalence data to determine the number of triple-class experienced HIV-1 patients. A range of assumptions, some of which are not verifiable or supported, are then used to determine the number of patients eligible for treatment with maraviroc over a time horizon of five years. There are some uncertainties in the proportions of patients assumed to be eligible for treatment and the total costs that are estimated to be involved.

9.2 Perspective and time horizon

The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years[3].

9.3 Data sources

9.3.1 Incident and prevalent cases

Based on the published prevalence data of diagnosed HIV infection in Wales in 2006, the total number of adult patients in Wales accessing HIV-related care is estimated as 30 per 100,000 (which the company estimates is equivalent to 884 adult patients)[26]. Of these, it is assumed that 67% (592) would receive three or more antiretroviral therapies, based on UK data from 2006[26]. Based on expert clinical opinion (no further details provided), it is assumed that this estimate would increase by 14% year on year, equating to an increase in patients from 592 to 770 patients in 2008. Furthermore, it is assumed that approximately 15% of patients receiving three or more antiretroviral therapies would be considered triple class experienced (no further details provided), equating to 115 patients in 2008[3].

Based on a continued assumption of a 14% year on year increase in these figures, it is estimated in the company submission that 115 patients in 2008 would be triple class experienced, rising to 195 in 2012[3].

9.3.2 Projected rate of adoption and market share

Uptake rates of 50% in 2008, rising to 100% in 2012 are assumed for patients who are triple-class experienced and have viral loads $\geq$1,000 copies/mL (as required for the Trofile™ assay)[3]. It appears that 13% of patients who are triple-class experienced are assumed to have viral loads $\geq$1,000 copies/mL, although the source of or justification for this estimate is not discussed. Of these patients, it is assumed that 56% will have CCR5-tropic virus only, as in the population that was screened for participation in the MOTIVATE studies. The company estimates that four patients would be eligible for maraviroc treatment in 2008, rising to 17 patients in 2012[3], although the method of estimating these is not clear from the data presented.

The extent to which patients would remain on treatment for five years would seem to be subject to some uncertainty.

9.3.3 Costs and resource use

A daily cost of £18.37 for maraviroc is assumed, as in the cost utility analysis[3]. There appears to be an error in the assumed annual cost of maraviroc, which is based on 48 weeks of treatment (336 days) rather than the full 365 days assumed for the annual cost of OBT. This would underestimate the net budget impact of maraviroc. There are too few details provided to determine the reliability of the estimated OBT costs (see section 8.7.1).

The total costs of the Trofile™ assay are based on the estimated number of triple-class experienced patients with viral loads ≥1,000 copies/mL and the rates of uptake of 50% in 2008, rising to 100% in 2012. The company submission reports the cost of each Trofile™ assay to be £150[3]. The approach taken in the budget impact analysis assumes that it is known which patients have a HIV RNA level ≥1,000 copies/mL before the Trofile™ test is administered.

9.4 Results

The results are presented as the cumulative cost of treatment in each year (as 65.3% of patients are assumed to receive treatment with maraviroc for five years). It should be noted that these estimates are based on what appears to be an underestimation of the costs of maraviroc in patients assumed to take the drug for longer than 48 weeks.

The net cost of maraviroc is estimated in the company submission to be £24,146 in 2008, rising to £258,089 in 2012. The costs of the Trofile™ assay are estimated to be £2,250 in 2008, rising to £3,750 in 2012[3].

No direct savings are identified with the introduction of maraviroc within NHS Wales[3].

9.5 Sensitivity analyses

No sensitivity analyses were conducted around the budget impact estimates.

9.6 Table of comparative unit costs

Maraviroc is the first CCR5 antagonist to reach the market. It should be taken as part of an antiretroviral combination regimen and should optimally be combined with other antiretrovirals to which the patient's virus is sensitive[1]. Another agent licensed for use in treatment-experienced patients and that is added to OBT is the integrase inhibitor raltegravir (Insentress®▼)[27].

Table 1. Comparative costs

	Example dose	Approximate drug acquisition cost per 30 days[22]
Maraviroc	300mg twice daily	£551.10
Raltegravir	400mg twice daily	£647.29
This table does not imply therapeutic equivalence of the agents or doses. These calculations are based on a VAT rate of 17.5% and do not take into account the recent drop in VAT to 15%.		

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- BHIVA issued updated guidelines on antiretroviral treatment of HIV-1 in adults online in May 2008[4], as discussed previously.
- The London New Drugs Group, on behalf of the HIV Drugs and Treatment sub group of the London HIV Consortium, issued a review of maraviroc before it had received a marketing authorisation[6]. This did not make any specific recommendations for its use.
- The Health Protection Agency, in collaboration with National Public Health Survey for Wales, conduct an annual survey (SOPHID) of all patients seen for HIV-related treatment or care[28].
- As maraviroc is intended for patients who are highly pre-treated and may have few therapeutic options available to them, it will be initiated by specialists and therefore would not be currently deemed suitable for shared care.

10.2 Previous AWMSG advice

- Enfuvirtide (Fuzeon®▼) – recommended for use within NHS Wales for the treatment of patients with HIV-1, with restrictions; May 2004[29].
- Emtricitabine (Emtriva®) – recommended for use within NHS Wales as an option for the treatment of HIV-1 infected adults in combination with other antiretroviral agents for use in treatment-naïve patients in line with current BHIVA guidelines; June 2007[30].
- Emtricitabine/tenofovir DF (Truvada®) – recommended for use within NHS Wales as an option for the treatment of HIV-1 infected adults who are treatment-naïve and in line with current BHIVA guidelines; June 2007[31].
- Darunavir (Prezista®▼) – recommended for use within NHS Wales for the treatment of HIV-1 infection in highly pre-treated adults who have failed more than one regimen containing a PI, and where resistance profiling suggests it is appropriate; August 2007[16].
- Tipranavir (Aptivus®▼) – recommended for use within NHS Wales for the treatment of HIV-1 infection, only for the treatment of highly pre-treated adult patients who have failed multiple PIs, and where resistance profiling suggests it is appropriate; August 2007[17].
- Raltegravir (Isentress®▼) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in treatment-experienced adults in accordance with BHIVA guidance; October 2008[32].
- Fixed dose abacavir and lamivudine (Kivexa®) – recommended as an option for use within NHS Wales in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents from 12 years of age. Use should be in accordance with the BHIVA guidance; October 2008[33].
- Atazanavir (Reyataz®▼) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-experienced patients, in accordance with BHIVA guidance; December 2008[34].
- Atazanavir (Reyataz®▼) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-naïve patients, in accordance with BHIVA guidance; December 2008[35].
- Efavirenz / emtricitabine / tenofovir disoproxil (as fumarate) (Atripla®) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in adults with virological suppression to HIV-1 RNA levels of < 50

copies/ml on their current combination antiviral therapy for more than three months and in accordance with current BHIVA guidance; February 2009[36].

10.3 Other points

- No further trial data is anticipated to be released within the next 6 to12 months in relation to the licensed indication[3]. Ongoing studies are investigating the safety of maraviroc in treatment-experienced patients and the immune response when adding maraviroc to combination antiretroviral therapy[37].
- Maraviroc has been studied in treatment-naive patients in combination with zidovudine/lamivudine, but only limited data are available for this unlicensed indication (see section 7.2)[15]. Studies are ongoing.

10.4 Patient organisation information

A patient organisation submission by the Terrence Higgins Trust was provided to AWMSG members.

GLOSSARY

Dual tropism:
Viruses that use both the CCR5 and CXCR4 co-receptors for entry[6].

Incidence:
The rate at which new cases occur in a population during a specified period[38].

Mixed tropism:
Presence of a mixture of pure CCR5, CXCR4 and/or dual tropic viruses[6].

Overall sensitivity score:
The total number of drugs in the OBT considered to be active by resistance testing[3].

Prevalence:
The proportion of a population that are cases at a point in time[38].

Tropism:
Refers to the co-receptor that a particular HIV-1 strain uses to mediate entry into a CD4 cell. HIV-1 that infects cells via the CCR5 co-receptor only are called CCR5-tropic, whereas virus that infects cells via the CXCR4 co-receptor only is termed CXCR4-tropic[6].

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APPENDIX 1. Additional Clinical Information

Table 1A. Prospective studies of maraviroc in treatment-experienced adults infected only with CCR5-tropic HIV-1

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (maraviroc + OBT versus placebo + OBT)
MOTIVATE 1 and 2 combined (24 week interim and 48 week results)						
1-3, 8	Randomised, double-blind, placebo controlled phase IIb/III trials. Conducted in USA, Canada, Puerto Rico, Australia and Europe.	Randomisation 1:2:2 (placebo+OBT: maraviroc OD+OBT: maraviroc BD+OBT) Maraviroc 300mg OD is not licensed and not considered further in table 648 patients randomised to BD or placebo: (MOTIVATE 1: 360; MOTIVATE 2: 288). 635 patients received at least one dose of study drug.	Age > 16 years Viral load ≥5,000 copies/mL. Stable/no ARV regimen for ≥4weeks. Genotypic/phenotypic resistance to 3 of 4 ARV drug classes or ARV experience >6 months with ≥3 of 4 ARV drug classes. Willing to remain on randomised treatment without change to OBT (except due to toxicity or treatment failure). No detection of CXCR4 tropic virus at baseline (dual/mixed)	Mean age: 46 years Male: 89% % White:Black:Other* = 85:12:3 Mean HIV-1 RNA: 4.86 $\log_{10}$ copies/mL Median CD4 count: 167-171 cells/mm^3 Patients (n [%]) with†: *GSS score 0* 102 [23.9] vs 51 [24.4] *GSS score 1* 138 [32.4] vs 53 [25.4] *GSS score 2* 80 [18.8] vs 41 [19.6] *GSS score ≥3* 104 [24.4] vs 59 [28.2]	Placebo + OBT (n=209) Maraviroc 300mg OD + OBT (not licensed, not considered) Maraviroc 150/300mg BD (dose adjusted) + OBT (n=426)	**24 week interim results:** **Primary endpoint:** • HIV-1 RNA change from baseline ($\log_{10}$ copies/mL): -1.96 vs -0.99 (difference -0.97; CI -1.24 to -0.71§) **Secondary endpoints:** • Patients with HIV-1 RNA <400 copies/mL (%): 61.0 vs 27.8 • Patients with HIV-1 RNA <50 copies/mL (%): 45.3 vs 23.0 • CD4 cell count change from baseline (cells/mm^3): 106.3 vs 57.4 **48 week results:** **Primary endpoint:** • HIV-1 RNA change from baseline ($\log_{10}$ copies/mL): -1.84 vs -0.78 (difference -1.05; CI -1.33 to -0.78§) **Secondary endpoints:** • Patients with HIV-1 RNA <400 copies/mL (%): 56.1 vs 22.5 (OR 4.76; CI 3.24 to 7.00§) • Patients with HIV-1 RNA <50 copies/mL (%): 45.5 vs 16.7 (OR 4.49; CI 2.96 to 6.83§) • CD4 cell count change from baseline¶ (cells/mm^3): 124.07 vs 60.93 (difference 63.13; CI 44.28 to 81.99§)
96 week results						
3, 9, 10	Extended open-label follow-up to 96 weeks of study		As above, with the exception of OBT substitutions being allowed in all arms		OBT alone (n=111) Maraviroc 150/300mg BD + OBT (n=259)	• Patients with HIV-1 RNA <400 copies/mL (%): as % of original population: 50 vs 7 • Patients with HIV-1 RNA <50 copies/mL (%): as % of original population: 40 vs 6 • CD4 cell count change from baseline**††(cells/mm^3) 187 vs 154 (n=227 and 15 respectively)

ARV= antiretroviral; BD= twice daily; CI= confidence interval; OBT= optimised background therapy; OD= once daily; OR= odds ratio; *Reported by study participants- 13% (including OD maraviroc group) were Hispanic or Latino and could be included in any of three groups; †= maraviroc + OBT versus placebo + OBT; §= p value <0.0001 and CI were 95% except for HIV-1 RNA change from baseline which was 97.5%; ¶= last observation carried forward approach to impute missing values; **= mean of all predose assessments; ††= only includes patients with a value at week 96.

Table 2A. Proportion of patients achieving <50 copies/mL at week 48 by subgroup (pooled studies MOTIVATE 1 and MOTIVATE 2, intention to treat [FAS] population)[1]

Subgroups	HIV-1 RNA <50 copies/mL	
	Maraviroc + OBT (N=426)	Placebo + OBT (N=209)
Baseline HIV-1 RNA		
<5.0 $\log_{10}$ copies/mL	58.4%	26.0%
≥5.0 $\log_{10}$ copies/mL	34.7%	9.5%
Baseline CD4 (cells/uL)		
<50	16.5	2.6
50-100	36.4	12.0
101-200	56.7	21.8
201-350	57.8	21.0
≥350	72.9	38.5
No. active antiretroviral drugs in OBT*†		
0	32.7%	2.0%
1	44.5%	7.4%
2	58.2%	31.7%
≥3	62%	38.6%

HIV= human immunodeficiency virus; No.= number; OBT= optimised background therapy; RNA= ribonucleic acid; * Discontinuations or virological failures considered as failures; †Based on Genotypic Susceptibility Score.